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(71) Applicant: MERCK SHARP & DOHME LIMITED [GB/GB]; Hertford Road, Hoddesdon, Hertfordshire EN11 9BU (GB).

(72) Inventors: BAKER, Raymond; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). CURTIS, Neil, Roy; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). KULAGOWSKI, Janusz, Jozef; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). LEESON, Paul, David; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). RIDGILL, Mark, Peter; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). SMITH, Adrian, Leonard; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).

(74) Agent: THOMPSON, John; Merck & Co., Inc., Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).

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(54) Title: PYRROLO-PYRIDINE DERIVATIVES

(57) Abstract

A class of pyrrolo[2,3-b]pyridine derivatives, substituted at the 3-position by a substituted piperazinylmethyl moiety, are antagonists of dopamine receptor subtypes within the brain, having a selective affinity for the dopamine D_4 receptor subtype over other dopamine receptor subtypes, and are accordingly of benefit in the treatment and/or prevention of psychotic disorders such as schizophrenia whilst manifesting fewer side-effects than those associated with classical neuroleptic drugs.

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PYRROLO-PYRIDINE DERIVATIVES

This invention relates to the use of a particular class of heteroaromatic compounds. More particularly, the invention is concerned with the use of substituted pyrrolo[2,3-b]pyridine derivatives which are antagonists of dopamine receptor subtypes within the brain and are therefore of benefit in the treatment and/or prevention of psychotic disorders such as schizophrenia.

The "dopamine hypothesis" of schizophrenia predicts an increased activity of dopamine neurotransmission in the disease. The hypothesis is supported by early observations that drugs, such as amphetamine, with dopamine agonist or dopamine-releasing properties are capable of eliciting a psychosis indistinguishable from acute paranoid schizophrenia.

Schizophrenia is a disorder which is conventionally treated with drugs known as neuroleptics. In the majority of cases, the symptoms of schizophrenia can be treated successfully with so-called "classical" neuroleptic agents such as haloperidol. Classical neuroleptics generally are antagonists at dopamine D_2 receptors. The fact that classical neuroleptic drugs have an action on dopamine receptors in the brain thus lends credence to the "dopamine hypothesis" of schizophrenia.

Molecular biological techniques have revealed the existence of several subtypes of the dopamine receptor. The dopamine D_1 receptor subtype has been shown to occur in at least two discrete forms. Two forms of the D_2 receptor subtype, and at least one form of the D_3 receptor subtype, have also been discovered. More recently, the D_4 (Van Tol et al., Nature (London), 1991,

350, 610) and D_5 (Sunahara et al., Nature (London), 1991, 350, 614) receptor subtypes have been described.

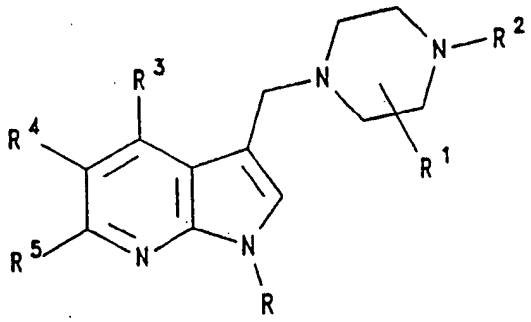
Notwithstanding their beneficial antipsychotic effects, classical neuroleptic agents such as haloperidol are frequently responsible for eliciting acute extrapyramidal symptoms and neuroendocrine disturbances. These side-effects, which clearly detract from the clinical desirability of classical neuroleptics, are believed to be attributable to D_2 receptor blockade in the striatal region of the brain. It is considered (Van Tol et al., supra) that compounds which can interact selectively with the dopamine D_4 receptor subtype, whilst having a less-pronounced action at the D_2 subtype, might be free from, or at any rate less prone to, the side-effects associated with classical neuroleptics, whilst at the same time maintaining a beneficial level of antipsychotic activity.

The compounds of use in the present invention, being antagonists of dopamine receptor subtypes within the brain, are accordingly of benefit in the treatment and/or prevention of psychotic disorders such as schizophrenia. Moreover, the compounds of use in the invention have a selective affinity for the dopamine D_4 receptor subtype over other dopamine receptor subtypes, in particular the D_2 subtype, and can therefore be expected to manifest fewer side-effects than those associated with classical neuroleptic drugs.

US Patents 3362956 and 3511841 describe certain 1-[(heterocyclyl)-lower-alkyl]-4-substituted-piperazines, in which the heterocyclyl moiety represents inter alia a pyrrolo[2,3-b]pyridine group (referred to therein as a 7-azaindole group). These compounds are alleged therein to possess a panoply of depressant actions on the autonomic nervous system, the cardiovascular system and the skeletal muscular system (including psychomotor

depressant, sedative, adrenolytic, rectal temperature lowering, anticonvulsant, blood pressure lowering and heart force increasing activities), and are consequently alleged to be useful as tranquilizers, sedatives, adrenolytic agents, hypothermic agents, anti-convulsants, hypotensive agents and cardiovascular agents. There is, however, no precise suggestion in US Patents 3362956 or 3511841 that the compounds described therein would be of any benefit in the treatment and/or prevention of psychotic disorders such as schizophrenia, still less that in doing so they might be expected to manifest fewer side-effects than those exhibited by classical neuroleptic agents.

The present invention accordingly provides the use of a compound of formula I, or a pharmaceutically acceptable salt thereof or a prodrug thereof:



(I)

wherein

R represents hydrogen or C_{1-6} alkyl;

R^1 represents hydrogen, or an optionally substituted C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, aryl(C_{1-6})alkyl, aryloxy(C_{1-6})alkyl, aryl(C_{1-6})alkoxy, aryl(C_{2-6})alkenyl, aryl(C_{2-6})alkynyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl, heteroaryl(C_{1-6})alkyl, heteroaryl(C_{2-6})alkenyl or

heteroaryl(C_{2-6})alkynyl group; or R^1 represents a straight or branched alkylene chain containing from 1 to 4 carbon atoms, and optionally incorporating an oxygen atom, which links the piperazine moiety to the group R^2;

R^2 represents an optionally substituted C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, aryl(C_{1-6})alkyl, aryloxy(C_{1-6})alkyl, aryl(C_{1-6})alkoxy, aryl(C_{2-6})alkenyl, aryl(C_{2-6})alkynyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl, heteroaryl(C_{1-6})alkyl, heteroaryl(C_{2-6})alkenyl or heteroaryl(C_{2-6})alkynyl group;

R^3, R^4 and R^5 independently represent hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, nitro, $-OR^a$, $-SR^a$, $-SOR^a$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aR^b$, $-NR^aCOR^b$, $-NR^aCO_2R^b$, $-COR^a$, $-CO_2R^a$ or $-CONR^aR^b$; and

R^a and R^b independently represent hydrogen, hydrocarbon or a heterocyclic group;

for the manufacture of a medicament for the treatment and/or prevention of psychotic disorders such as schizophrenia.

Also of use in accordance with the present invention are the compounds of formula I above wherein R^1 is other than a straight or branched alkylene chain containing from 1 to 4 carbon atoms, and optionally incorporating an oxygen atom, which links the piperazine moiety to the group R^2; and the remaining substituents are as defined with reference to formula I above.

For use in medicine, the salts of the compounds of formula I will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds of use in the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of use in this invention include acid addition salts which may,

for example, be formed by mixing a solution of the compound of use in the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compounds of use in the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

The term "hydrocarbon" as used herein includes straight-chained, branched and cyclic groups containing up to 18 carbon atoms, suitably up to 15 carbon atoms, and conveniently up to 12 carbon atoms. Suitable hydrocarbon groups include C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, aryl, aryl(C_{1-6})alkyl, aryl(C_{2-6})alkenyl and aryl(C_{2-6})alkynyl.

The expression "a heterocyclic group" as used herein includes cyclic groups containing up to 18 carbon atoms and at least one heteroatom preferably selected from oxygen, nitrogen and sulphur. The heterocyclic group suitably contains up to 15 carbon atoms and conveniently up to 12 carbon atoms, and is preferably linked through carbon. Examples of suitable heterocyclic groups include C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl, heteroaryl(C_{1-6})alkyl, heteroaryl(C_{2-6})alkenyl and heteroaryl(C_{2-6})alkynyl groups.

Suitable alkyl groups within the scope of the term "hydrocarbon" and within the definition of the substituents R, R^1 and R^2 include straight-chained and

branched alkyl groups containing from 1 to 6 carbon atoms. Typical examples include methyl and ethyl groups, and straight-chained or branched propyl and butyl groups. Particular alkyl groups are methyl, ethyl, n-propyl, isopropyl and t-butyl.

Suitable alkenyl groups within the scope of the term "hydrocarbon" and within the definition of the substituents R^1 and R^2 include straight-chained and branched alkenyl groups containing from 2 to 6 carbon atoms. Typical examples include vinyl and allyl groups.

Suitable alkynyl groups within the scope of the term "hydrocarbon" and within the definition of the substituents R^1 and R^2 include straight-chained and branched alkynyl groups containing from 2 to 6 carbon atoms. Typical examples include ethynyl and propargyl groups.

Suitable cycloalkyl groups include groups containing from 3 to 7 carbon atoms. Particular cycloalkyl groups are cyclopropyl and cyclohexyl.

Particular aryl groups within the scope of the term "hydrocarbon" and within the definition of the substituents R^1 and R^2 include phenyl and naphthyl.

Particular aryl(C_{1-6})alkyl groups within the scope of the term "hydrocarbon" and within the definition of the substituents R^1 and R^2 include benzyl, naphthylmethyl, phenethyl and phenylpropyl.

Suitable heterocycloalkyl groups include azetidinyl, pyrrolidyl, piperidyl, piperazinyl, morpholinyl and tetrahydrofuryl groups.

A particular C_{3-7} heterocycloalkyl(C_{1-6})alkyl group within the scope of the expression "a heterocyclic group" and within the definition of the substituents R^1 and R^2 is tetrahydrofurylethyl.

Suitable heteroaryl groups within the scope of the expression "a heterocyclic group" and within the

definition of the substituents R^1 and R^2 include pyridyl, quinolyl, isoquinolyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyranyl, furyl, benzofuryl, dibenzofuryl, thienyl, benzthienyl, indolyl, indazolyl, imidazolyl, benzimidazolyl, oxadiazolyl and thiadiazolyl groups.

Particular heteroaryl(C_{1-6})alkyl groups within the scope of the expression "a heterocyclic group" and within the definition of the substituents R^1 and R^2 include thienylmethyl, pyridylmethyl, pyrimidinylmethyl and pyrazinylmethyl.

The hydrocarbon and heterocyclic groups, as well as the substituents R^1 and R^2, may in turn be optionally substituted by one or more groups selected from C_{1-6} alkyl, adamantyl, phenyl, aryl(C_{1-6})alkyl, halogen, halo(C_{1-6})alkyl, amino(C_{1-6})alkyl, C_{1-6} alkylamino(C_{1-6})alkyl, di(C_{1-6})alkylamino(C_{1-6})alkyl, trifluoromethyl, hydroxy, hydroxy(C_{1-6})alkyl, C_{1-6} alkoxy, C_{1-6} alkoxy(C_{1-6})alkyl, aryloxy, keto, C_{1-3} alkylenedioxy, nitro, cyano, carboxy, C_{2-6} alkoxycarbonyl, C_{2-6} alkoxycarbonyl(C_{1-6})alkyl, C_{2-6} alkylcarbonyloxy, arylcarbonyloxy, C_{2-6} alkylcarbonyl, arylcarbonyl, C_{1-6} alkylthio, C_{1-6} alkylsulphinyl, C_{1-6} alkylsulphonyl, arylsulphonyl, trifluoromethanesulphonyloxy, $-NR^VR^W$, $-NR^VCOR^W$, $-NR^VCO_2R^W$, $-NR^VSO_2R^W$, $-CH_2NR^VSO_2R^W$, $-NHCONR^VR^W$, $-PO(OR^V)(OR^W)$, $-CONR^VR^W$, $-SO_2NR^VR^W$ and $-CH_2SO_2NR^VR^W$, in which R^V and R^W independently represent hydrogen, C_{1-6} alkyl, aryl or aryl(C_{1-6})alkyl.

The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, especially chlorine.

The present invention includes within its scope the use of prodrugs of the compounds of formula I above. In general, such prodrugs will be functional derivatives of the compounds of formula I which are readily

convertible in vivo into the required compound of formula I. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

Where the compounds of use in the invention have at least one asymmetric centre, they may accordingly exist as enantiomers. Where the compounds of use in the invention possess two or more asymmetric centres, they may additionally exist as diastereoisomers. It is to be understood that the use of all such isomers and mixtures thereof is encompassed within the scope of the present invention.

Suitably, the substituent R represents hydrogen or methyl, especially hydrogen.

Suitably, the substituent R^1 represents hydrogen, fluoro or chloro, especially hydrogen.

When R^1 represents a straight or branched alkylene chain containing from 1 to 4 carbon atoms, and optionally incorporating an oxygen atom, which links the piperazine moiety to the group R^2, this is suitably a methylene, ethylene or oxamethylene chain.

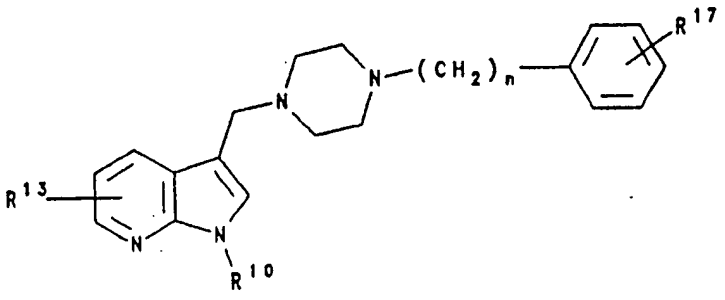
Suitable values for the substituent R^2 include C_{1-6} alkyl, aryl, aryl(C_{1-6})alkyl, aryloxy(C_{1-6})alkyl and heteroaryl, any of which groups may be optionally substituted. Examples of optional substituents on the group R^2 include C_{1-6} alkyl, halogen, trifluoromethyl, hydroxy, hydroxy(C_{1-6})alkyl, C_{1-6} alkoxy, C_{1-6} alkoxy(C_{1-6})alkyl, C_{1-3} alkylenedioxy, carboxy, C_{2-6} alkoxycarbonyl, nitro, C_{1-6} alkylamino, di(C_{1-6})alkylamino, C_{1-6} alkylamino(C_{1-6})alkyl and di(C_{1-6})alkylamino(C_{1-6})alkyl.

Particular values of R^2 include methyl, ethyl, n-propyl, isopropyl, phenyl, methylphenyl, ethylphenyl, fluorophenyl, chlorophenyl, dichlorophenyl, bromophenyl,

iodophenyl, trifluoromethyl-phenyl, hydroxyphenyl, hydroxymethyl-phenyl, methoxyphenyl, ethoxyphenyl, methoxymethyl-phenyl, methylenedioxy-phenyl, carboxyphenyl, methoxycarbonyl-phenyl, ethoxycarbonyl-phenyl, nitrophenyl, dimethylamino-phenyl, dimethylaminomethyl-phenyl, benzyl, chlorobenzyl, phenethyl, phenoxy-ethyl, methylpyridyl, chloropyridyl, isoquinolyl, indolyl, methylindolyl, indazolyl and benzthienyl.

Suitable values for the substituents R^3, R^4 and R^5 include hydrogen, halogen, cyano, nitro, trifluoromethyl, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, C_{1-6} alkyl, C_{1-6} alkoxy, aryl(C_{1-6})alkoxy and C_{2-6} alkylcarbonyl. Particular values include hydrogen, fluoro, chloro, methyl, methoxy and benzyloxy.

A particular sub-class of compounds of use in the invention is represented by the compounds of formula IIA, and pharmaceutically acceptable salts thereof and prodrugs thereof:



(IIA)

wherein

n is zero, 1, 2 or 3;

R^{10} represents hydrogen or methyl, especially hydrogen;

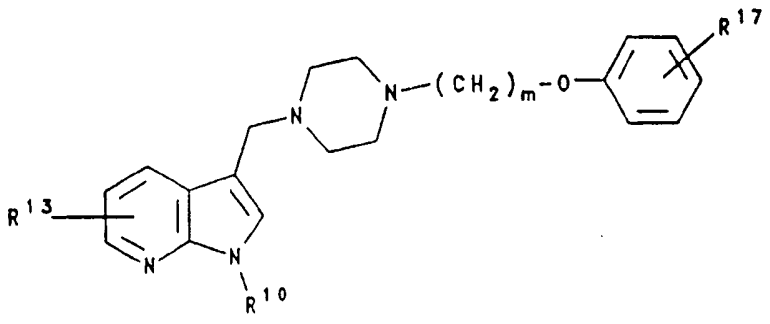
R^{13} represents hydrogen, halogen, cyano, nitro, trifluoromethyl, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, C_{1-6} alkyl, C_{1-6} alkoxy, aryl(C_{1-6})alkoxy or C_{2-6} alkylcarbonyl; and

R^{17} represents hydrogen, C_{1-6} alkyl, halogen, trifluoromethyl, hydroxy, hydroxy(C_{1-6})alkyl, C_{1-6} alkoxy, aryl(C_{1-6})alkoxy, C_{1-6} alkoxy(C_{1-6})alkyl, carboxy, C_{2-6} alkoxycarbonyl, C_{2-6} alkylcarbonyl, cyano, nitro, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, amino(C_{1-6})alkyl, C_{1-6} alkylamino(C_{1-6})alkyl or di(C_{1-6})alkylamino(C_{1-6})alkyl.

Particular values of R^{13} include hydrogen, fluoro, chloro, methyl, ethyl, methoxy and benzyloxy, especially hydrogen.

Particular values of R^{17} include hydrogen, methyl, ethyl, fluoro, chloro, bromo, iodo, trifluoromethyl, hydroxy, hydroxymethyl, methoxy, ethoxy, methoxymethyl, carboxy, methoxycarbonyl, ethoxycarbonyl, nitro, dimethylamino and dimethylaminomethyl.

Another sub-class of compounds of use in the invention is represented by the compounds of formula IIB, and pharmaceutically acceptable salts thereof and prodrugs thereof:



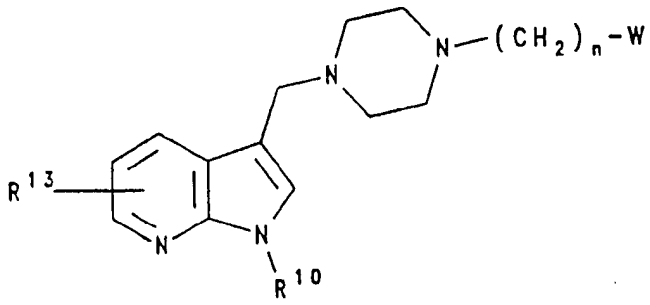
(IIB)

wherein

m is 1, 2 or 3; and

R^{10}, R^{13} and R^{17} are as defined with reference to formula IIA above.

A further sub-class of compounds of use in the invention is represented by the compounds of formula IIC, and pharmaceutically acceptable salts thereof and prodrugs thereof:

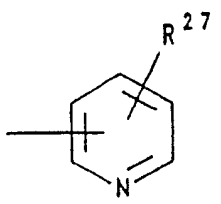


(IIC)

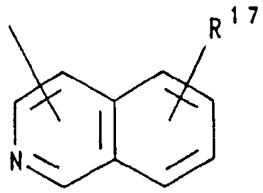
wherein

n, R^{10} and R^{13} are as defined with reference to formula IIA above; and

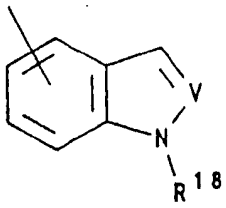
W represents a group of formula (i), (ii), (iii) or (iv):



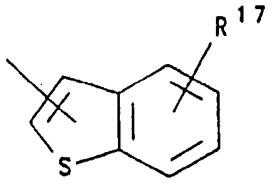
(I)



(II)



(III)



(IV)

in which

V represents nitrogen or CH;

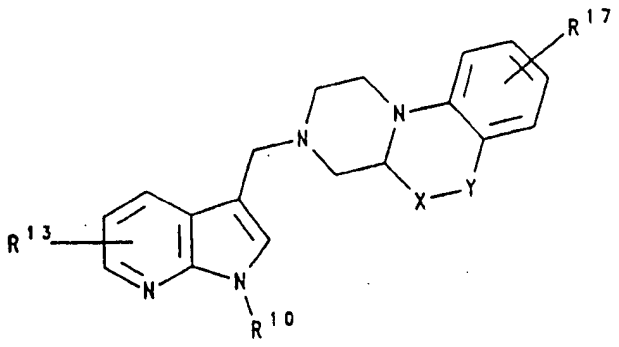
R^{17} is as defined with reference to formula IIA above;

R^{18} represents hydrogen or methyl; and

R^{27} represents C_{1-6} alkyl, halogen, trifluoromethyl, C_{1-6} alkoxy, cyano, nitro, amino, C_{1-6} alkylamino or di(C_{1-6})alkylamino.

Suitably, R^{27} is C_{1-6} alkyl or halogen, especially methyl or chloro.

A still further sub-class of compounds of use in the invention is represented by the compounds of formula IID, and pharmaceutically acceptable salts thereof and prodrugs thereof:



(IID)

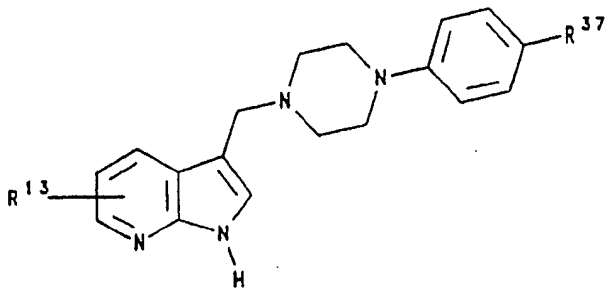
wherein

X represents a group of formula $-CH_2-$ or $-CH_2CH_2-$;

Y represents a chemical bond or an oxygen atom; and

R^{10}, R^{13} and R^{17} are as defined with reference to formula IIA above.

Certain compounds falling within the scope of formula I above are novel. Particular sub-classes of novel compounds in accordance with the present invention comprise the compounds of formula IIB, IIC and IID as defined above, and salts and prodrugs thereof. A discrete sub-class of novel compounds according to the invention having particularly advantageous properties as selective antagonists of the dopamine D_4 receptor subtype relative to the D_2 subtype, and hence as agents for the treatment and/or prevention of psychotic disorders such as schizophrenia which manifest fewer side-effects than those associated with classical neuroleptic drugs, comprises the compounds of formula IIE, and salts and prodrugs thereof:



(IIE)

wherein

R^{13} is as defined with reference to formula IIA above; and

R^{37} represents fluoro, chloro, bromo, iodo or trifluoromethyl.

The invention further provides a novel compound selected from the following:

3-(4-phenylpiperazin-1-yl)methyl-1H-pyrrolo[2,3-b]-pyridine;

3-[4-(4-methoxyphenyl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;

3-(4-benzylpiperazin-1-yl)methyl-1H-pyrrolo[2,3-b]-pyridine;

3-[4-(4-ethylphenyl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;

3-[4-(4-chlorophenyl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;

3-[4-(4-ethoxyphenyl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;

3-[4-(4-dimethylaminophenyl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;

3-[4-(3,4-dichlorophenyl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;

3-[4-(4-methoxyphenyl)piperazin-1-yl]methyl-1-methyl-1H-pyrrolo[2,3-b]pyridine;

3-[4-(5-chloropyrid-2-yl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(3-isoquinolyl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(5-indolyl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(4-iodophenyl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(4-trifluoromethylphenyl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(2-phenoxyethyl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(4-methylphenyl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(4-fluorophenyl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(1-methylindol-5-yl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(indazol-5-yl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(4-ethoxycarbonylphenyl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(4-carboxyphenyl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(3-methylphenyl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(2-methylphenyl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(3,4-methylenedioxyphenyl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(4-bromophenyl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(4-methoxycarbonylphenyl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;

3-[4-(4-hydroxymethylphenyl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(5-methylpyrid-2-yl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(4-hydroxyphenyl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(benzothiophen-2-yl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(benzothiophen-3-yl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[(1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]-2,3,4,4a,5,6-hexahydro-1(H)-pyrazino[1,2-a]quinoline;
8-chloro-3-[(1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]-2,3,4,4a,5,6-hexahydro-1(H)-pyrazino[1,2-a]quinoline;
8-chloro-3-[(1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]-2,3,4,4a,5,6-hexahydro-1(H)-pyrazino[2,1-c]-1,4-benzoxazine;
3-[4-(4-methoxymethylphenyl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(4-dimethylaminomethylphenyl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-(1,2,3,4,10,10a-hexahydropyrazino[1,2-a]indol-2-yl)methyl-1H-pyrrolo[2,3-b]pyridine;
and salts and prodrugs thereof.

The invention also provides pharmaceutical compositions comprising one or more of the novel compounds according to the invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation.

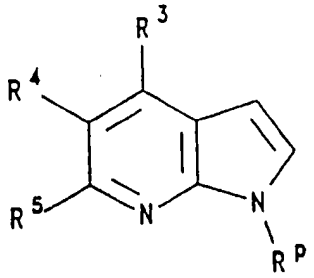
Alternatively, the compositions may be presented in a form suitable for once-weekly or once-monthly administration; for example, an insoluble salt of the active compound, such as the decanoate salt, may be adapted to provide a depot preparation for intramuscular injection. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of

polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

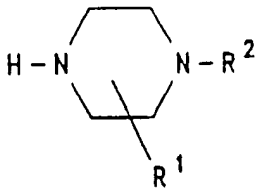
The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

In the treatment of schizophrenia, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.05 to 100 mg/kg per day, and especially about 0.05 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day.

The compounds of formula I above, including the novel compounds according to the present invention, may be prepared by a process which comprises reacting a compound of formula III with a compound of formula IV:



(III)



(IV)

wherein R^1, R^2, R^3, R^4 and R^5 are as defined above, and R^P corresponds to the group R as defined above or represents a suitable protecting group; in the presence of a substantially equimolar amount of formaldehyde; followed, where required, by removal of the protecting group R^P; and subsequently, if necessary, N-alkylation by standard methods to introduce the moiety R.

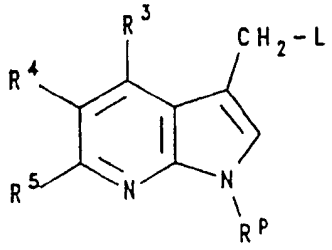
The reaction is conveniently carried out by stirring the reactants in aqueous acetic acid, ideally in the presence of a buffer such as sodium acetate trihydrate, suitably at room temperature.

The formaldehyde may be utilised in the form of paraformaldehyde; or as a solution of formaldehyde in an inert solvent, e.g. 37% aqueous formaldehyde.

The protecting group R^P, when present, is suitably an acyl moiety such as acetyl, which can conveniently be removed as necessary by treatment under strongly basic conditions, e.g. sodium methoxide in methanol. Alternatively, the protecting group R^P may be a carbamoyl moiety such as t-butoxycarbonyl (BOC), which can conveniently be removed as necessary by treatment under mildly acidic conditions.

In an alternative procedure, the compounds of formula I above, including the novel compounds according

to the present invention, may be prepared by a process which comprises reacting a compound of formula IV as defined above with a compound of formula V:



(V)

wherein R^3, R^4, R^5 and R^P are as defined above, and L represents a suitable leaving group; followed, where required, by removal of the protecting group R^P; and subsequently, if necessary, N-alkylation by standard methods to introduce the moiety R.

The leaving group L is suitably a halogen atom, e.g. chlorine or bromine; or a dialkylamino group, e.g. dimethylamino.

When L represents a halogen atom, the reaction between compounds IV and V is conveniently carried out by stirring the reactants under basic conditions in a suitable solvent, for example potassium carbonate in N,N-dimethylformamide, or triethylamine in tetrahydrofuran or acetonitrile. Where L represents a dialkylamino group, the reaction is conveniently effected by heating the reactants in an inert solvent such as toluene, typically at the reflux temperature of the solvent.

Where they are not commercially available, the starting materials of formula III, IV and V may be prepared by procedures analogous to those described in the accompanying Examples, or by standard methods well known from the art.

It will be appreciated that any compound of formula I initially obtained from any of the above processes may, where appropriate, subsequently be elaborated into a further desired compound of formula I using techniques known from the art. For example, a compound of formula I wherein R is hydrogen initially obtained may be converted into a compound of formula I wherein R represents C_{1-6} alkyl by standard alkylation techniques, such as by treatment with an alkyl iodide, e.g. methyl iodide, typically under basic conditions, e.g. sodium hydride in dimethylformamide, or triethylamine in acetonitrile. Moreover, a compound of formula I wherein the R^2 moiety is substituted by carboxy may be obtained from the corresponding alkyl ester derivative initially obtained by conventional deesterification procedures, typically by treatment with a base such as sodium hydroxide in a lower alkanol such as ethanol. Similarly, a compound of formula I wherein the R^2 moiety is substituted by an alkyl ester or carboxamide moiety initially obtained may be converted into the corresponding hydroxymethyl or aminomethyl derivative respectively by reduction with an appropriate reducing agent, e.g. diisobutylaluminium hydride or lithium aluminium hydride.

Where the above-described processes for the preparation of the compounds of use in the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The compounds may, for example, be resolved into their component enantiomers by standard techniques such as preparative HPLC, or the formation of diastereomeric pairs by salt formation with an optically active acid,

such as (-)-di-p-toluoyl-d-tartaric acid and/or (+)-di-p-toluoyl-l-tartaric acid, followed by fractional crystallization and regeneration of the free base. The compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The following Examples illustrate the preparation of compounds according to the invention.

The compounds useful in this invention potently inhibit [^{3}H]-spiperone binding to human dopamine D_4 receptor subtypes expressed in clonal cell lines.

[^{3}H]-Spiperone Binding Studies

Clonal cell lines expressing the human dopamine D_4 receptor subtype were harvested in PBS and then lysed in 10 mM Tris-HCl pH 7.4 buffer containing 5 mM $MgSO_4$ for 20 min on ice. Membranes were centrifuged at 50,000g for 15 min at 4°C and the resulting pellets resuspended in assay buffer (50 mM Tris-HCl pH 7.4 containing 5 mM EDTA, 1.5 mM $CaCl_2$, 5 mM $MgCl_2$, 5 mM KCl, 120 mM NaCl, and 0.1% ascorbic acid) at 20 mg/ml wet weight. Incubations were carried out for 60 min at room temperature (22°C) in the presence of 0.05-2 nM [^{3}H]-spiperone or 0.2 nM for

displacement studies and were initiated by addition of 20-100 μg protein in a final assay volume of 0.5 ml. The incubation was terminated by rapid filtration over GF/B filters presoaked in 0.3% PEI and washed with 10 ml ice-cold 50 mM Tris-HCl, pH 7.4. Specific binding was determined by 10 μM apomorphine and radioactivity determined by counting in a LKB beta counter. Binding parameters were determined by non-linear least squares regression analysis, from which the inhibition constant K_i could be calculated for each test compound.

The compounds of the accompanying Examples were tested in the above assay, and all were found to possess a K_i value for displacement of [^{3}H]-spiperone from the human dopamine D_4 receptor subtype of below 1.5 μM.

EXAMPLE 1

3-(4-Phenylpiperazin-1-yl)methyl-1H-pyrrolo[2,3-b]pyridine

1-Phenylpiperazine (1.63g, 10.0mmol), and sodium acetate trihydrate (1.36g, 10mmol) were dissolved in acetic acid (4ml) and water (2ml). 37% Aqueous formaldehyde (0.9ml, 12mmol) was added and the reaction mixture stirred for five minutes. 1H-Pyrrolo[2,3-b]pyridine (1.18g, 10mmol) was added, and the resulting solution stirred at room temperature overnight. The reaction mixture was poured into 2M sodium hydroxide solution (50ml) and extracted with ethyl acetate (2 x 50ml). The extracts were washed with brine (50ml), combined and dried ($MgSO_4$). The ethyl acetate solution was concentrated *in vacuo* to about one quarter of the original volume and the precipitated yellow solid was collected by filtration and recrystallised from toluene to yield the *title compound* (1.20g), as pale lemon crystals. This material was further recrystallised from methanol to give pale lemon needles, m.p. 207-209°C; (Found: C, 73.91; H, 7.09; N, 19.31. $C_{18}H_{20}N_4$ requires C, 73.94; H, 6.90; N, 19.16%); δ_H (DMSO-d_6) 2.53 (4H, t, J 5Hz, 2 x CH_2N), 3.10 (4H, t, J 5Hz, 2 x CH_2N), 3.68 (2H, s, indole-CH_2N), 6.75 (1H, t, J 7Hz, 4'-H), 6.89 (2H, d, J 8Hz, 2'-H, 6'-H), 7.04 (1H, dd, J 8, 4.5Hz, 5-H), 7.18 (2H, t, J 8Hz, 3'-H, 5'-H), 8.05 (1H, dd, J 8, 1.5Hz, 4-H), 8.19 (1H, dd, J 4.5, 1.5Hz, 6-H), and 11.45 (1H, br s, NH); m/z (CI^+, NH_3) 293 $(M+1)^+$.

Prepared in an analogous manner were:

EXAMPLE 2

3-(4-[4-Methoxyphenyl]piperazin-1-yl)methyl-1H-pyrrolo [2,3-b]pyridine

M.p. 213-214°C (PhMe); (Found: C, 70.84; H, 6.75; N, 17.14. $C_{19}H_{22}N_4O$ requires C, 70.78; H, 6.88; N, 17.38%); δ_H (DMSO-d_6) 2.49-2.53 (4H, m, 2 x piperazinyl CH_2), 2.98 (4H, m, 2 x piperazinyl CH_2), 3.66-3.67 (5H, m, CH_2 + OCH_3), 6.77-6.86 (4H, m, ArH), 7.04 (1H, dd, J 7.9, 4.6Hz, 5-H), 7.37 (1H, d, J 1.6Hz, ArH), 8.04 (1H, dd, J 7.9, 1.5Hz, 4-H), 8.19 (1H, dd, J 4.6, 1.5Hz, 6-H), and 11.46 (1H, br s, NH); m/z (CI^+, NH_3) 323 $(M+1)^+$.

EXAMPLE 3

3-(4-Benzylpiperazin-1-yl)methyl-1H-pyrrolo[2,3-b]pyridine

M.p. 153°C (MeOH); (Found: C, 74.35; H, 7.03; N, 18.17. $C_{19}H_{22}N_4$ requires C, 74.48; H, 7.24; N, 18.29%); δ_H (DMSO-d_6) 2.36 (8H, br s, 4 x CH_2), 3.42 (2H, s, CH_2), 3.60 (2H, s, CH_2), 7.01 (1H, dd, J 7.8, 4.6Hz, 5-H), 7.19-7.31 (6H, m, ArH), 8.01 (1H, dd, J 7.8, 1.5Hz, 4-H), 8.17 (1H, dd, J 4.6, 1.5Hz, 6-H), and 11.41 (1H, br s, NH); m/z (CI^+, NH_3) 307 (M+1).

EXAMPLE 4

3-(4-[4-Ethylphenyl]piperazin-1-yl)methyl-1H-pyrrolo [2,3-b]pyridine

M.p. 216-217°C (MeOH); (Found: C, 75.32; H, 7.36; N, 17.59. $C_{20}H_{24}N_4$ requires C, 74.97; H, 7.55; N, 17.48%); δ_H (DMSO-d_6) 1.12 (3H, t, J 7.6Hz, $ArCH_2CH_3$), 2.50 (6H, m, $ArCH_2CH_3$ and 2 x

piperazinyl CH_2), 3.05 (4H, m, 2 x piperazinyl CH_2), 3.67 (2H, s, N-$C\underline{H}_2$Ar), 6.81 (2H, d, J 8.6Hz, ArH), 7.03 (3H, m, ArH), 7.37 (1H, d, J 2.2Hz, 2-H), 8.05 (1H, dd, J 7.8, 1.4Hz, 4-H), 8.19 (1H, dd, J 4.6, 1.4Hz 6-H), and 11.47 (1H, br s, NH); m/z (CI^+, NH_3) 321 $(M+1)^+$.

EXAMPLE 5

3-(4-[4-Chlorophenyl]piperazin-1-yl)methyl-1H-pyrrolo [2,3-b]pyridine

M.p. 226-227°C (MeOH); (Found: C, 65.77; H, 5.78; N, 17.26. $C_{18}H_{19}N_4Cl$ requires C, 66.15; H, 5.86; N, 17.14%); δ_H (DMSO-d_6) 2.53 (4H, m, 2 x piperazinyl CH_2), 3.10 (4H, m, 2 x piperazinyl CH_2), 3.67 (2H, s, CH_2-N), 6.90 (2H, d, J 9.0Hz, ArH), 7.03 (1H, dd, J 7.8, 4.6Hz, 5-H), 7.19 (2H, d, J 9.0Hz, ArH), 7.37 (1H, d, J 2.4Hz, 2-H), 8.04 (1H, dd, J 7.8, 1.6Hz, 4-H), 8.19 (1H, dd, J 4.6, 1.6Hz, 6-H), and 11.47 (1H, br s, NH); m/z (CI^+, NH_3) 327 $(M+1)^+$.

EXAMPLE 6

3-(4-[4-Ethoxyphenyl]piperazin-1-yl)methyl-1H-pyrrolo[2,3-b] pyridine

Step 1: 1-(*tert*-Butoxycarbonyl)-4-(4-hydroxyphenyl)piperazine

Di-*tert*-butyl dicarbonate (3.13g, 14.3mmol) was added to a suspension of 1-(4-hydroxyphenyl)piperazine (2.40g, 13.5mmol) in dichloromethane (60ml) and the mixture stirred overnight at room temperature. The reaction mixture was filtered and the filtrate evaporated. Trituration with diethyl ether gave 1-(*tert*-

butoxycarbonyl)-4-(4-hydroxyphenyl)piperazine as a buff solid (2.76g, 74%); δ_H ($CDCl_3$) 1.48 (9H, s, $C(CH_3)_3$), 2.99 (4H, m, 2 x piperazinyl CH_2), 3.58 (4H, m, 2 x piperazinyl CH_2), 5.18 (1H, br s, ArOH), 6.77 (2H, m, ArH), and 6.85 (2H, m, ArH).

Step 2: 1-(4-Ethoxyphenyl)piperazine

Bromoethane (0.48ml, 6.43mmol) was added to a mixture of 1-(*tert*-butoxycarbonyl)-4-(4-hydroxyphenyl)piperazine (1.64g, 5.89mmol) and potassium carbonate (0.90g, 6.51mmol) in dimethylformamide (15ml). The reaction mixture was stirred overnight and then more potassium carbonate (1.63g, 11.8mmol) and bromoethane (0.48ml, 6.43mmol) was added. The mixture was stirred at room temperature overnight, poured into water (150ml) and extracted with ethyl acetate (2 x 100ml). The extracts were washed with brine (100ml), combined, and dried ($MgSO_4$). Evaporation of the solvent gave a buff solid (1.71g). This was dissolved in dichloromethane (20ml), trifluoroacetic acid (10ml) added and the reaction mixture stirred at room temperature under nitrogen for 30 minutes. The mixture was concentrated *in vacuo*, the residue dissolved in 1M hydrochloric acid (50ml) and washed with dichloromethane (2 x 25ml). The aqueous phase was basified with 4M sodium hydroxide (30ml) and extracted with ethyl acetate (2 x 50ml). The extracts were washed with brine (50ml), combined, dried ($MgSO_4$) and concentrated *in vacuo* to give *1-(4-ethoxyphenyl) piperazine* (1.03g, 89%) as a beige solid; δ_H ($CDCl_3$) 1.38 (3H, t, J 7.0Hz, $ArCH_2\underline{CH_3}$), 1.84 (1H, br s, NH), 3.04 (8H, s, 4 x piperazinyl CH_2), 3.98 (2H, q, J 7.0Hz, $Ar\underline{CH_2}CH_3$), and 6.82-6.91 (4H, m, ArH).

Step 3: 3-(4-[4-Ethoxyphenyl]piperazin-1-yl)methyl-1H-pyrrolo[2,3-b]pyridine

A mixture of 3-dimethylaminomethyl-1H-pyrrolo[2,3-b]pyridine [prepared by the method of M.M. Robison and B.L. Robison, J. Am. Chem. Soc., 1955, 77, 457] (0.40g, 2.28mmol) and 1-(4-ethoxyphenyl)piperazine (0.495g, 2.40mmol) in toluene (10ml) was heated at reflux under nitrogen for 7h. The mixture was allowed to cool and the crystallised product collected. Recrystallisation from methanol afforded the *title compound* (0.513g, 67%), m.p. 179-180°C; (Found: C, 71.27; H, 7.19; N, 16.59. $C_{20}H_{24}N_4O$ requires C, 71.40; H, 7.19; N, 16.65%); δ_H (DMSO-d_6) 1.27 (3H, t, J 7.0Hz, $ArOCH_2\underline{CH_3}$), 2.52 (4H, m, 2 x piperazinyl CH_2), 2.98 (4H, m, 2 x piperazinyl CH_2), 3.67 (2H, s, CH_2N), 3.92 (2H, q, J 7.0Hz, $ArO\underline{CH_2}CH_3$), 6.80 (4H, m, ArH), 7.04 (1H, dd, J 7.8, 4.6Hz, 5-H), 7.37 (1H, d, J 2.1Hz, 2-H), 8.04 (1H, dd, J 7.8, 1.3Hz, 4-H), 8.19 (1H, dd, J 4.6, 1.3Hz, 6-H), and 11.46 (1H, br s, NH); m/z (CI^+, NH_3) 337 $(M+1)^+$.

EXAMPLE 7

3-(4-[4-Dimethylaminophenyl]piperazin-1-yl)methyl-1H-pyrrolo[2,3-b]pyridine

Step 1: 1-(*tert*-Butoxycarbonyl)-4-(4-dimethylaminophenyl)piperazine

Di-*tert*-butyl dicarbonate (3.11g, 14.2mmol) was added to a solution of 1-(4-nitrophenyl)piperazine (2.96g, 14.3mmol) in dichloromethane (100ml). The resulting solution was stirred for 3h at room temperature and then concentrated *in vacuo* to a yellow solid (4.37g). The solid was dissolved in ethanol (200ml), a 37% aqueous solution of formaldehyde

(3.2ml, 43mmol) and 10% palladium on carbon (0.40g) were added and the mixture hydrogenated on a Parr apparatus (maximum 50psi) for 8h. Further portions of aqueous formaldehyde (1.0ml) and 10% palladium on carbon (0.10g) were added and the reaction mixture hydrogenated overnight. This procedure was repeated to ensure complete formation of the desired product. The reaction mixture was filtered and the filtrate concentrated to an oil which was treated with silica gel in ethyl acetate. The mixture was filtered and concentrated to give *1-(tert-butoxycarbonyl)-4-(4-dimethylaminophenyl)piperazine* (4.25g, 98%) as an off-white crystalline solid; δ_H (DMSO-d_6) 1.41 (9H, s, $C(CH_3)_3$), 2.78 (6H, s, $N(CH_3)_2$), 2.89 (4H, m, 2 x piperazinyl CH_2), 3.44 (4H, m, 2 x piperazinyl CH_2), 6.68 (2H, m, ArH), and 6.84 (2H, m, ArH).

Step 2: 1-(4-Dimethylaminophenyl)piperazine

Trifluoroacetic acid (10ml) was added to a solution of 1-(*tert*-butoxycarbonyl)-4-(4-dimethylaminophenyl)piperazine (2.01g 6.58mmol) in dichloromethane (20ml) and the mixture stirred for 30 min at room temperature. The mixture was concentrated *in vacuo* and saturated aqueous potassium carbonate (100ml) was cautiously added to the residue. The mixture was extracted with dichloromethane (3 x 100ml), the extracts were washed with brine (50ml), combined and dried ($MgSO_4$). Concentration of the extracts gave *1-(4-dimethylaminophenyl)piperazine* (1.14g, 84%) as a cream solid; δ_H (DMSO-d_6) 2.77 (6H, s, $N(CH_3)_2$), 2.79 (4H, m, 2 x piperazinyl CH_2), 2.86 (4H, m, 2 x piperazinyl CH_2), 6.68 (2H, m, ArH), and 6.82 (2H, m, ArH).

Step 3: 3-(4-[4-Dimethylaminophenyl]piperazin-1-yl)methyl-1H-pyrrolo[2,3-b]pyridine

A mixture of 3-dimethylaminomethyl-1H-pyrrolo[2,3-b]pyridine (0.4450g, 2.54mmol) and 1-(4-dimethylaminophenyl)piperazine (0.55g, 2.68mmol) in toluene (20ml) was heated at reflux under nitrogen for 7h. The mixture was allowed to cool and the solid formed was collected. Recrystallisation from methanol gave the *title compound* (0.382g, 45%) as colourless needles, m.p. 199-201°C; (Found: C, 71.32; H, 7.37; N, 20.71. $C_{20}H_{25}N_5$ requires C, 71.61; H, 7.51; N, 20.88%); δ_H (DMSO-d_6) 2.52 (4H, m, 2 x piperazinyl CH_2), 2.76 (6H, s, $N(CH_3)_2$), 2.95 (4H, m, 2 x piperazinyl CH_2), 3.67 (2H, s, CH_2N), 6.66 (2H, m, ArH), 6.80 (2H, m, ArH), 7.03 (1H, dd, J 7.8, 4.7Hz), 7.35 (1H, d, J 2.0Hz, 2-H), 8.04 (1H, dd, J 7.8, 1.5Hz, 4-H), 8.19 (1H, dd, J 4.7, 1.5Hz, 6-H), and 11.41 (1H, br s, NH); m/z (CI^+, NH_3) 336 $(M+1)^+$.

EXAMPLE 8

3-(4-[3,4-Dichlorophenyl]piperazin-1-yl)methyl-1H-pyrrolo [2,3-b]pyridine

M.p. 219-220°C (MeOH); (Found: C, 60.05; H, 5.18; N, 15.32. $C_{18}H_{18}Cl_2N_4$ requires C, 59.84; H, 5.02; N, 15.51%); δ_H (DMSO-d_6) 2.50 (4H, m, 2 x piperazinyl CH_2), 3.15 (4H, m, 2 x piperazinyl CH_2), 3.67 (2H, s, CH_2N), 6.89 (1H, dd, J 2.9,9.0Hz, 6′-H), 7.04 (1H, dd, J 7.8, 4.7Hz, 5-H), 7.09 (1H, d, J 2.9Hz, 2′-H), 7.36 (2H, m, 2-H, 5′-H), 8.05 (1H, dd, J 7.8, 1.5Hz, 4-H), 8.20 (1H, dd, J 4.7, 1.5Hz, 6-H), 11.48 (1H, br s, NH); m/z (CI^+, NH_3) 361 $[(M+1)^+, {}^{35}Cl_2]$.

EXAMPLE 9

3-(4-[4-Methoxyphenyl]piperazin-1-yl)methyl-1-methyl-1H-pyrrolo[2,3-b]pyridine

Sodium hydride (80% dispersion in oil; 0.13g, 4.3mmol) was added to a solution of 3-(4-(4-methoxyphenyl)piperazin-1-yl)methyl-1H-pyrrolo[2,3-b]pyridine (1.06g, 3.29mmol) in dimethylformamide (30ml) at 0°C. The cooling bath was removed and the mixture stirred at room temperature for an hour. Methyl iodide (0.22ml, 3.53mmol) was added and the reaction mixture stirred for 2h at room temperature. The mixture was poured into water (300ml), extracted with ethyl acetate (2 x 150ml), and the extracts washed with brine (150ml). The combined extracts were dried ($MgSO_4$) and evaporated to give a yellow solid. Purification by flash chromatography, eluting with 5% then 7.5% methanol in dichloromethane, gave the *title compound* (0.87g, 79%). Recrystallisation from ethyl acetate/petrol (60-80°C) gave fine needles, m.p. 92-94°C; (Found: C, 71.25; H, 7.18; N, 16.49. $C_{20}H_{24}N_4O$ requires C, 71.40; H, 7.19; N, 16.65%); δ_H ($CDCl_3$) 2.65 (4H, m, 2 x piperazinyl CH_2), 3.09 (4H, m, 2 x piperazinyl CH_2), 3.74 (2H, s, CH_2N), 3.75 (3H, s, $ArOCH_3$), 3.87 (3H, s, N-CH_3), 6.85 (4H, m, ArH), 7.05 (1H, dd, J 7.8, 4.7Hz, 5-H), 7.15 (1H, br s, 2-H), 8.04 (1H, dd, J 7.8, 1.5Hz, 4-H), and 8.33 (1H, dd, J 4.7, 1.5Hz, 6-H); m/z (CI^+, NH_3) 337 $(M+1)^+$.

EXAMPLE 10

3-(4-[5-Chloro-2-pyridyl]piperazin-1-yl)methyl-1H-pyrrolo [2,3-b]pyridine

A mixture of 2,5-dichloropyridine (10.0g, 67.6mmol) and piperazine (58.1g, 675mmol) was stirred at 165°C for 2h. The mixture was allowed to cool, slurried with dichloromethane (200ml) and the solid collected by filtration. The filtrate was concentrated *in vacuo* and the procedure repeated. The residue after concentration of the filtrate was purified by flash chromatography twice (eluting with 1% ammonia, 10% methanol in dichloromethane) to give 1-(5-chloro-2-pyridyl)piperazine (12.25g, 92%) as a tan solid. A portion of this solid (0.484g, 2.45mmol) was added to a solution of 3-dimethylaminomethyl-1H-pyrrolo[2,3-b] pyridine (0.392g, 2.24mmol) in toluene (10ml) and the mixture heated at reflux under nitrogen for 6h. The mixture was allowed to cool and the crystallised product filtered off. Recrystallisation from toluene gave the *title compound* (0.229g, 31%), m.p. 196-198°C; (Found: C, 63.16; H, 5.60; N, 21.18. $C_{17}H_{18}ClN_5$. 0.1PhMe requires C, 63.08; H, 5.62; N, 20.78%); δ_H (DMSO-d_6) 2.46 (4H, t, J 5.0Hz, 2 x piperazinyl CH_2), 3.45 (4H, t, J 5.0Hz, 2 x piperazinyl CH_2), 3.67 (2H, s, CH_2N), 6.82 (1H, d, J 9.1Hz, 3'-H), 7.04 (1H, dd, J 7.8, 4.6Hz, 5-H), 7.37 (1H, d, J 2.1Hz, 2-H), 7.56 (1H, dd, J 9.1, 2.7Hz, 4'-H), 8.05 (1H, dd, J 7.8, 1.4Hz, 4-H), 8.08 (1H, d, J 2.7Hz, 6'-H), 8.19 (1H, dd, J 4.6, 1.4Hz, 6-H), and 11.46 (1H, br s, NH); m/z (CI^+, NH_3) 328 [$(M+H)^+$, ^{35}Cl].

EXAMPLE 11

3-(4-[3-Isoquinolyl]piperazin-1-yl)methyl-1H-pyrrolo [2,3-b]pyridine

Prepared by the method outlined in the previous example from the trifluoromethanesulphonate derived from 3-hydroxyisoquinoline.

M.p. 246-248°C (dec.) (EtOH); (Found: C, 72,15; H, 6.11; N, 19.92. $C_{21}H_{21}N_5 . 0.35H_2O$ requires C, 72.12; H, 6.25; N, 20.02%); δ_H (DMSO-d_6) 2.55 (4H, m, 2 x piperazinyl CH_2), 3.51 (4H, m, 2 x piperazinyl CH_2), 3.70 (2H, s, CH_2N), 6.94 (1H, s, 4′-H), 7.05 (1H, dd, J 7.8, 4.7Hz, 5-H), 7.28 (1H, m, 6′-H or 7′-H), 7.39 (1H, s, 2-H), 7.52 (1H, m, 7′-H or 6′H), 7.64 (1H, m, 5′-H or 8′-H), 7.85 (1H, m, 8′-H or 5′-H), 8.08 (1H, dd, J 7.8, 1.5Hz, 4-H), 8.20 (1H, dd, J 4.7, 1.5Hz, 6-H), and 11.48 (1H, br s, NH); m/z (CI^+, NH_3) 344 $(M+1)^+$.

EXAMPLE 12

3-(4-[5-Indolyl]piperazin-1-yl)methyl-1H-pyrrolo[2,3-b]pyridine

Step 1: 1-(5-Indolyl)piperazine

Bis(2-chloroethyl)amine hydrochloride (3.60g, 20.2mmol) was added to a suspension of 5-aminoindole (2.53g, 19.1mmol) in ethanol (30ml) and the mixture heated at reflux for 16h. The mixture was allowed to cool, sodium carbonate (2.14g, 20.2mmol) was added and the reaction mixture heated at reflux for 8h. The mixture was allowed to cool, filtered and the filtrate evaporated. The residue was dissolved in 1M hydrochloric acid (100ml) and extracted with dichloromethane (2 x 50ml). The aqueous phase was made basic

with 4M sodium hydroxide (30ml) and extracted with ethyl acetate (2 x 100ml). The extracts were washed with brine (100ml), combined and dried ($MgSO_4$). The residue from evaporation of the extracts was purified by flash chromatography, eluting with dichloromethane/methanol/ammonia, to give *1-(5-indolyl)piperazine* (0.71g, 18%), as a cream solid; δ_H (DMSO-d_6) 2.94 (4H, m, 2 x piperzinyl CH_2), 3.00 (4H, m, 2 x piperazinyl CH_2), 6.29 (1H, m, 3-H), 6.84 (1H, dd, J 9.0,2.0Hz, 6-H), 7.00 (1H, d, J 2.0Hz, 2-H), 7.24 (2H, m, 4-H, 7-H), and 10.82 (1H, br s, NH).

Step 2: 3-(4-[5-Indolyl]piperazin-1-yl)methyl-1H-pyrrolo [2,3-b]pyridine

A mixture of 3-dimethylaminomethyl-1H-pyrrolo[2,3-b] pyridine (0.23g, 1.33mmol) and 1-(5-indolyl)piperazine (0.27g, 1.34mmol) in toluene (20ml) was heated at reflux for 16h under nitrogen. The mixture was allowed to cool and the solid present collected. Purification by flash chromatography, eluting with 90:8:1 dichloromethane/methanol/ammonia, twice gave the *title compound* (0.14g, 32%) as a white solid. Recrystallisation from methanol afforded needles, m.p. 232.5-233°C; (Found: C, 72.14; H, 6.29; N, 21.07. $C_{20}H_{21}N_5$. $0.1H_2O$ requires C, 72.09; H, 6.41; N, 21.02%); δ_H (DMSO-d_6) 2.56 (4H, m, 2 x piperazinyl CH_2), 3.02 (4H, m, 2 x piperazinyl CH_2), 3.69 (1H, s, CH_2N), 6.27 (1H, m, 3′-H), 6.83 (1H, dd, J 8.8, 2.1Hz, 6′-H), 6.97 (1H, m, 2′-H), 7.05 (1H, dd, J 7.8, 4.6Hz, 5-H), 7.22 (2H, m, 4′-H, 7′-H), 7.38 (1H, d, J 2.1Hz, 2-H), 8.06 (1H, dd, J 7.8, 1.4Hz, 4-H), 8.20 (1H, dd, J 4.6, 1.4Hz, 6-H), 10.77 (1H, br s, NH), and 11.46 (1H, br s NH); m/z (CI^+, NH_3) 322 $(M+1)^+$.

EXAMPLE 13

3-(4-[4-Iodophenyl]piperazin-1-yl)methyl-1H-pyrrolo [2,3-b]pyridine

M.p. 223-225°C (dec.) (MeOH); (Found: C, 51.85; H, 4.50; N, 13.12. $C_{18}H_{19}N_4I$ requires C, 51.69; H, 4.58; N, 13.39%); δ_H (DMSO-d_6) 2.50 (4H, m, 2 x piperazinyl CH_2), 3.10 (4H, m, 2 x piperazinyl CH_2), 3.67 (2H, s, CH_2N), 6.74 (2H, d, J 9.0Hz, ArH), 7.04 (1H, dd, J 7.8, 4.7Hz, 5-H), 7.37 (1H, d, J 2.0Hz, 2-H), 7.46 (2H, d, J 9.0Hz, ArH), 8.05 (1H, dd, J 7.8, 1.4Hz, 4-H), 8.19 (1H, dd, J 4.7, 1.4Hz, 6-H), and 11.47 (1H, br s, NH); m/z (CI^+, NH_3) 419 $(M+1)^+$.

EXAMPLE 14

3-(4-[4-(Trifluoromethyl)phenyl]piperazin-1-yl)methyl-1H-pyrrolo[2,3-b]pyridine

M.p. 247-250°C (dec.) (MeOH); (Found: C, 63.44; H, 5.29; N, 15.38. $C_{19}H_{19}F_3N_4$ requires C, 63.32; H, 5.31; N, 15.55%); δ_H (DMSO-d_6) 2.51 (4H, m, 2 x piperazinyl CH_2), 3.26 (4H, m, 2 x piperazinyl CH_2), 3.68 (2H, s, CH_2N), 7.04 (3H, m, 5-H + 2 x ArH), 7.38 (1H, br s, 2-H), 7.48 (2H, d, J 8.6Hz, ArH), 8.05 (1H, br d, J 8Hz, 4-H), 8.20 (1H, m, 6-H), and 11.47 (1H, br s, NH); m/z CI^+, NH_3) 361 $(M+1)^+$.

EXAMPLE 15

3-(4-[2-Phenoxyethyl]piperazin-1-yl)methyl-1H-pyrrolo [2,3-b]pyridine

M.p. 143°C (EtOAc); (Found: C, 71.39; H, 7.19; N, 16.35. $C_{20}H_{24}N_4O$ requires C, 71.40; H, 7.19; H, 16.65%); δ_H (DMSO-d_6) 2.40 (4H, br s, 2 x CH_2), 2.47 (4H, br s, 2 x CH_2), 2.66 (2H, t, J 5.8Hz, NCH_2CH_2O), 3.60 (2H, s, CH_2), 4.03 (2H, t, J 5.8Hz, NCH_2CH_2O), 6.89 (3H, m, ArH), 7.03 (H, dd, J 7.8, 4.7Hz, 5-H), 7.26 (2H, t, J 3.4Hz, ArH), 7.32 (1H, d, 2.1Hz, 2-H), 8.00 (H, dd, J 7.8, 1.2Hz, 4-H), 8.18 (H, dd, J 4.7, 1.5Hz, 6-H), and 11.42 (H, br s, NH); m/z (CI^+, NH_3) 337 (M+1).

EXAMPLE 16

3-(4-[4-Methylphenyl]piperazin-1-yl)methyl-1H-pyrrolo [2,3-b]pyridine

M.p. 220-222°C (MeOH); (Found: C, 74.24; H, 7.12; N, 18.32. $C_{19}H_{22}N_4$ requires: C, 74.48; H, 7.24; N, 18.29%); δ_H (DMSO-d_6) 2.18 (3H, s, $ArCH_3$), 2.04-2.53 (4H, m, 2 x piperazinyl CH_2), 3.04 (4H, t, J 4.8Hz, 2 x piperazinyl CH_2), 3.67 (2H, s, NCH_2Ar), 5.79 (2H, d, J 8.5Hz, ArH), 6.99 (2H, d, J 8.5Hz, ArH), 7.03 (1H, dd, J 7.8, 4.7Hz, 5-H), 7.36 (1H, d, J 2.2Hz, 2-H), 8.04 (1H, dd, J 7.8, 1.3Hz, 4-H), 8.19 (1H, dd, J 4.7, 1.5Hz, 6-H), and 11.45 (1H, br s, N-H); m/z (CI^+, NH_3) 307 $(M+1)^+$.

EXAMPLE 17

3-(4-[4-Fluorophenyl]piperazin-1-yl)methyl-1H-pyrrolo[2,3-b]pyridine

M.p. 214-216°C (MeOH); (Found: C, 69.42; H, 6.29; N, 17.91. $C_{18}H_{19}N_4F$ requires C, 69.66; H, 6.17; N, 18.05%); δ_H (DMSO-d_6) 2.49-2.53 (4H, m, 2 x piperazinyl CH_2), 3.04 (4H, t, J 4.8Hz, 2 x piperazinyl CH_2), 3.68 (2H, s, NCH_2Ar), 6.88-6.93 (2H, m, ArH), 6.98-7.05 (3H, m, ArH), 7.37 (1H, d, J 2.3Hz, 2-H), 8.04 (1H, dd, J 7.8, 1.3Hz, 4-H), 8.19 (1H, dd, J 4.7, 1.5Hz, 6-H), and 11.47 (1H, br s, NH); m/z (CI^+, NH_3) 311 $(M+1)^+$.

EXAMPLE 18

3-(4-[1-Methyl-5-indolyl]piperazin-1-yl)methyl-1H-pyrrolo[2,3-b]pyridine

Step 1: 1-(*tert*-Butoxycarbonyl)-4-(1-methyl-5-indolyl)piperazine

Di-*tert*-butyldicarbonate (0.46g, 2.11mmol) was added to a solution of 1-(5-indolyl)piperazine (0.41g, 2.04mmol) in dimethylformamide/tetrahydrofuran (1:1; 20ml) and the mixture stirred at room temperature overnight. The mixture was poured into water (200ml) and extracted with ethyl acetate (2 x 100ml). The extracts were washed with brine (100ml), combined and dried ($MgSO_4$). The residue after evaporation of the solvent was dissolved in tetrahydrofuran (5ml). Sodium hydride (80% dispersion in oil; 0.068g, 2.27mmol) was added and the mixture stirred at room temperature for thirty minutes. Methyl iodide (0.14ml, 2.25mmol)

was added, the reaction mixture was stirred for 90 minutes then poured into water (50ml) and extracted with ethyl acetate (2 x 50ml). The extracts were washed with brine (50ml), combined and dried ($MgSO_4$). Purification of the residue by flash chromatography, eluting with 1:3 then 1:2 ethyl acetate/petrol, gave the *title compound* (0.218g, 34%) as a waxy solid; δ_H ($CDCl_3$) 1.49 (9H, s, $C(CH_3)_3$), 3.08 (4H, t, J 4.8Hz, 2 x piperazinyl CH_2), 3.62 (4H, t, J 4.8Hz, 2 x piperazinyl CH_2), 3.76 (3H, s, N-CH_3), 6.39 (1H, d, J 3.0Hz, 3'-H), 7.00 (2H, m, 2-H, 5-H), and 7.24 (1H, d, J 9.1Hz, 7-H).

Step 2: 3-(4-[1-Methyl-5-indolyl]piperazin-1-yl)methyl-1H-pyrrolo[2,3-b]pyridine

Trifluoroacetic acid (5ml) was added to a solution of 1-(*tert*-butoxycarbonyl)-4-(1-methyl-5-indolyl)piperazine (0.2102g, 0.666mmol) in dichloromethane (5ml) and the mixture stirred for 30 minutes at room temperature. The mixture was concentrated *in vacuo* and saturated aqueous potassium carbonate (20ml) was added to the residue. The mixture was extracted with dichloromethane (2 x 20ml), the extracts washed with brine (20ml), combined and dried ($MgSO_4$). The extracts were concentrated and the residual yellow solid redissolved in toluene (5ml). 3-Dimethylaminomethyl-1H-pyrrolo[2,3-b]pyridine (0.1136g, 0.648mmol) was added and the mixture heated at reflux under nitrogen for 5 hours. The mixture was allowed to cool and the solid present collected. Purification by flash chromatography, eluting with 120:8:1 then 90:8:1 dichloromethane/methanol/ammonia, gave the *title compound* (0.1433g, 64%) as a yellow solid. Recrystallisation from methanol afforded pale yellow needles, m.p. 222-223°C; (Found: C, 72.81; H, 6.81; N, 20.17. $C_{21}H_{23}N_5$ requires C, 73.02; H, 6.71; N, 20.27%); δ_H (DMSO-d_6) 2.57 (4H, m, 2 x piperazinyl CH_2), 3.03 (4H, m, 2 x

piperazinyl CH_2), 3.69 (2H, s, CH_2N), 3.71 (3H, s, N-CH_3), 6.25 (1H, d, J 2.9Hz, 3'-H), 6.89 (1H, dd, J 8.9, 2.1Hz, 6'-H), 6.98 (1H, d, J 2.0Hz, 2-H or 4'-H), 7.05 (1H, dd, J 7.8, 4.6Hz, 5-H), 7.18 (1H, d, J 2.9Hz, 2'-H), 7.26 (1H, d, J 8.9Hz, 7'-H), 7.38 (1H, d, J 2.1Hz, 4'-H or 2-H), 8.07 (1H, dd, J 7.8, 1.4Hz, 4-H), 8.20 (1H, dd, J 4.6, 1.4Hz, 6-H), and 11.46 (1H, br s, NH); m/z (CI^+, NH_3) 346 $(M+1)^+$.

EXAMPLE 19

3-(4-[5-Indazolyl]piperazin-1-yl)methyl-1H-pyrrolo[2,3-b]pyridine

Prepared in an analogous manner to 3-(4-[5-indolyl]piperazin-1-yl)methyl-1H-pyrrolo[2,3-b]pyridine (Example 12).

M.p. 238-239.5°C (dec.) (MeOH); (Found: C, 68.39; H, 6.07; N, 25.34. $C_{19}H_{20}N_6$ requires C, 68.65; H, 6.06; N, 25.28%); δ_H (DMSO-d_6) 2.57 (4H, m, 2 x piperazinyl CH_2), 3.06 (4H, m, 2 x piperazinyl CH_2), 3.70 (2H, s, CH_2N), 7.05 (2H, m, 5-H, 4'-H), 7.15 (1H, dd, J 9.1, 2.1Hz, 6'-H), 7.38 (2H, m, 2-H, 7'-H), 7.87 (1H, s, 3'-H), 8.06 (1H, dd, J 7.8, 1.4Hz, 4-H), 8.20 (1H, dd, J 4.7, 1.5Hz, 6-H), 11.48 (1H, br s, NH), and 12.77 (1H, br s, NH); m/z (CI^+, NH_3) 333 $(M+1)^+$.

EXAMPLE 20

3-(4-[4-Ethoxycarbonylphenyl]piperazin-1-yl)methyl-1H-pyrrolo[2,3-b]pyridine

M.p. 196-197°C (EtOH); (Found: C, 69.04; H, 6.57; N, 15.20. $C_{21}H_{24}N_4O_2$ requires C, 69.21; H, 6.64; N, 15.37%); δ_H (DMSO-d_6)

1.28 (3H, t, J 7.1Hz, OCH_2CH_3), 2.50 (4H, m, 2 x piperazinyl CH_2), 3.30 (4H, m, 2 x piperazinyl CH_2), 3.69 (2H, s, CH_2N), 4.23 (2H, q, J 7.1Hz, OCH_2CH_3), 6.94 (2H, d, J 9.0Hz, ArH), 7.04 (1H, dd, J 7.8, 4.6Hz, 5-H), 7.38 (1H, d, J 2.2Hz, 2-H), 7.76 (2H, d, J 9.0Hz, ArH), 8.05 (1H, dd, J 7.8, 1.4Hz, 4-H), 8.20 (1H, dd, J 4.6, 1.4Hz, 6-H), and 11.47 (1H, br s, NH); m/z (CI^+, NH_3) 365 $(M+1)^+$.

EXAMPLE 21

3-(4-[4-Carboxyphenyl]piperazin-1-yl)methyl-1H-pyrrolo[2,3-b]pyridine

A suspension of 3-(4-[4-ethoxycarbonylphenyl]piperazin-1-yl)methyl-1H-pyrrolo[2,3-b]pyridine (0.6594g, 1.81mmol) in ethanol (50ml) containing 1M aqueous sodium hydroxide (10.5ml, 10.8mmol) was stirred at room temperature for eight days, during which time the solid slowly dissolved. The reaction mixture was concentrated to a small volume, diluted with water and neutralised (pH 6-7) with acetic acid to give a gum which solidified on standing. The solid was collected, washed with water and dried *in vacuo*. Recrystallisation from dimethylformamide/water gave the *title compound* (0.4069g, 67%) as a white solid, m.p. >250°C (dec.); (Found: C, 66.96; H, 5.88; N, 16.30. $C_{19}H_{20}N_4O_2.0.25H_2O$ requires C, 66.94; H, 6.06; N, 16.44); δ_H (DMSO-d_6) 2.51 (4H, m, 2 x piperazinyl CH_2), 3.27 (4H, m, 2 x piperazinyl CH_2), 3.68 (2H, s, CH_2N), 6.93 (2H, d, J 9.0Hz, ArH), 7.04 (1H, dd, J 7.8, 4.7Hz, 5-H), 7.38 (1H, d, J 2.2Hz, 2-H), 7.57 (2H, d, J 9.0Hz, ArH), 8.06 (1H, dd, J 7.8, 1.4Hz, 4-H), 8.20 (1H, dd, J 4.7, 1.4Hz, 6-H), and 11.48 (1H, br s, NH); m/z (CI^+, NH_3) 337 $(M+1)^+$.

EXAMPLE 22

3-(4-[3-Methylphenyl]piperazin-1-yl)methyl-1H-pyrrolo[2,3-b]pyridine

M.p. 156-158°C (MeOH); (Found: C, 73.73; H, 7.12; N, 17.99. $C_{19}H_{22}N_4.0.2H_2O$ requires C, 73.61; H, 7.28; N, 18.07%); δ_H (DMSO-d_6) 2.22 (3H, s, $ArCH_3$), 2.51 (4H, m, 2 x piperazinyl CH_2), 3.09 (4H, m, 2 x piperazinyl CH_2), 3.67 (2H, s, CH_2N), 6.57 (1H, m, ArH), 6.70 (2H, m, ArH), 7.05 (2H, m, 5-H, ArH), 7.38 (1H, d, J 2.3Hz, 2-H), 8.05 (1H, m, 4-H), 8.19 (1H, dd, J 4.6, 1.5Hz, 6-H), and 11.48 (1H, br s, NH); m/z (CI^+, NH_3) 307 $(M+1)^+$.

EXAMPLE 23

3-(4-[2-Methylphenyl]piperazin-1-yl)methyl-1H-pyrrolo[2,3-b]pyridine

M.p. 174-176°C (MeOH); (Found: C, 74.29; H, 7.18; N, 18.11. $C_{19}H_{22}N_4$ requires C, 74.48; H, 7.24; N, 18.29%); δ_H (DMSO-d_6) 2.21 (3H, s, $ArCH_3$), 2.55 (4H, br s, 2 x piperazinyl CH_2), 2.81 (4H, m, 2 x piperazinyl CH_2), 3.70 (2H, s, CH_2N), 6.92 (1H, m, ArH), 6.99 (1H, m, ArH), 7.04 (1H, dd, J 7.8, 4.7Hz, 5-H), 7.09 (2H, m, ArH), 7.37 (1H, d, J 2.2Hz, 2-H), 8.06 (1H, dd, J 7.8, 1.3Hz, 4-H), 8.20 (1H, dd, J 4.7, 1.5Hz, 6-H), and 11.46 (1H, br s, NH); m/z (CI^+, NH_3) 307 $(M+1)^+$.

EXAMPLE 24

3-(4-[3,4-Methylenedioxyphenyl]piperazin-1-yl)methyl-1H-pyrrolo[2,3-b]pyridine

M.p. 196-199°C (PhMe); (Found: C, 67.69; H, 6.03; N, 16.48. $C_{19}H_{20}N_4O_2$ requires C, 67.84; H, 5.99; N, 16.66%); δ_H (DMSO-d_6) 2.50 (4H, m, 2 x piperazinyl CH_2), 2.98 (4H, m, 2 x piperazinyl CH_2), 3.67 (2H, s, CH_2N), 5.89 (2H, s, OCH_2O), 6.30 (1H, dd, J 8.5, 2.3Hz, 6'-H), 6.62 (1H, d, J 2.3Hz, 2'-H), 6.73 (1H, d, J 8.5Hz, 5'-H), 7.04 (1H, dd, J 7.8, 4.6Hz, 5-H), 7.36 (1H, br s, 2-H), 8.04 (1H, m, 4-H), 8.19 (1H, m, 6-H), and 11.43 (1H, br s, NH); m/z (CI^+, NH_3) 337 $(M+1)^+$.

EXAMPLE 25

3-(4-[4-Bromophenyl]piperazin-1-yl)methyl-1H-pyrrolo[2,3-b]pyridine

M.p. 234-238°C (MeOH); (Found: C, 57.89; H, 5.10; N, 14.86. $C_{18}H_{19}BrN_4$ requires C, 58.23; H, 5.16; N, 15.09%); δ_H (DMSO-d_6) 2.50 (4H, m, 2 x piperazinyl CH_2), 3.10 (4H, m, 2 x piperazinyl CH_2), 3.67 (1H, s, CH_2N), 6.85 (2H, d, J 9.0Hz, ArH), 7.04 (1H, dd, J 7.8, 4.7Hz, 5-H), 7.31 (2H, d, J 9.0Hz, ArH), 7.37 (1H, d, J 2.3Hz, 2-H), 8.04 (1H, dd, J 7.8, 1.4Hz, 4-H), 8.19 (1H, dd, J 4.7, 1.5Hz, 6-H), and 11.45 (1H, br s, NH); m/z (CI^+, NH_3) 373/371 $(M+1)^+$.

EXAMPLE 26

3-(4-[4-Methoxycarbonylphenyl]piperazin-1-yl)methyl-1H-pyrrolo[2,3-b]pyridine

M.p. 205-207°C (dec.) (PhMe); (Found: C, 67.94; H, 6.27; N, 15.70. $C_{20}H_{22}N_4O_2.0.15H_2O$ requires C, 68.03; H, 6.37; N, 15.87%); δ_H (DMSO-d_6) 2.50 (4H, m, 2 x piperazinyl CH_2), 3.29 (4H, m, 2 x

piperazinyl CH_2), 3.68 (2H, s, CH_2N), 3.76 (3H, s, CO_2CH_3), 6.94 (2H, d, J 9.1Hz, ArH), 7.05 (1H, dd, J 7.8, 4.7Hz, 5-H), 7.38 (1H, d, J 2.1Hz, 2-H), 7.76 (2H, d, J 9.1Hz, ArH), 8.06 (1H, br d, J 7.8Hz, 4-H), 8.22 (1H, dd, J 4.7, 1.5Hz, 6-H), and 11.48 (1H, br s, NH); m/z (CI+, NH_3) 351 $(M+1)^+$.

EXAMPLE 27

3-(4-[4-Hydroxymethylphenyl]piperazin-1-yl)methyl-1H-pyrrolo[2,3-b]pyridine

A solution of diisobutylaluminium hydride in toluene (1.5M, 9.4ml, 14.1mmol) was added to a solution of 3-(4-[4-methoxycarbonylphenyl]piperazin-1-yl)methyl-1H-pyrrolo[2,3-b]pyridine (1.64g, 4.68mmol) in tetrahydrofuran (100ml) and the resultant mixture stirred at room temperature for forty minutes. Methanol (3.3ml) was added, followed by water (2.0ml) and 2M aqueous sodium hydroxide (2.0ml). The precipitate formed was collected, the filtrate concentrated *in vacuo* and the solid residue was recrystallised from methanol to afford the *title compound* (1.12g, 74%), m.p. 207-209°C (dec.); (Found: C, 69.48; H, 7.00; N, 16.61. $C_{19}H_{22}N_4O.0.3$ MeOH requires C, 69.82; H, 7.04; N, 16.87%); δ_H (DMSO-d_6) 2.52 (4H, m, 2 x piperazinyl CH_2), 3.08 (4H, m, 2 x piperazinyl CH_2), 3.68 (2H, CH_2N), 4.36 (2H, d, J 5.6Hz, $C\underline{H}_2OH$), 4.92 (1H, t, J 5.6Hz, $CH_2O\underline{H}$), 6.85 (2H, d, J 8.7Hz, ArH), 7.05 (1H, dd, J 7.9, 4.7Hz, 5-H), 7.13 (2H, d, J 8.7Hz, ArH), 7.37 (1H, d, J 2.2Hz, 2-H), 8.05 (1H, br d, J 7.9Hz, 4-H), 8.19 (1H, dd, J 4.7, 1.5Hz, 6-H), and 11.47 (1H, br s, NH); m/z (CI+, NH_3) 323 $(M+1)^+$.

EXAMPLE 28

3-(4-[5-Methyl-2-pyridyl]piperazin-1-yl)methyl-1H-pyrrolo[2,3-b]pyridine

Bromine (74g, 24ml, 0.46mmol) was added dropwise with vigorous stirring to a solution of 2-amino-5-picoline (20.0g, 0.19mol) in 48% hydrobromic acid (300ml) at -10°C. Sodium nitrite (32g, 0.46mol) in water (80ml) was added dropwise to the orange suspension, maintaining the temperature below -5°C, and the mixture was then stirred at room temperature for 30 minutes. The mixture was recooled to 0°C and sodium hydroxide (188g, 4.7mol) in water (160ml) added dropwise. The resulting black suspension was extracted with ether (2 x 500ml), the extracts combined, dried ($MgSO_4$), and evaporated to give *2-bromo-5-picoline* as a tan solid (24g, 75%); δ_H ($CDCl_3$) 2.30 (3H, s, CH_3), 7.38 (2H, s, 3-H, 4-H), 8.21 (1H, s, 6-H). This was converted in two steps, using the procedure outlined in Example 10, to the *title compound*, m.p. 204-205°C (EtOAc); (Found: C, 70.53; H, 6.86; N, 22.86. $C_{18}H_{21}N_5$ requires C, 70.33; H, 6.89; N, 22.78%); δ_H (DMSO-d_6) 2.12 (3H, s, $ArCH_3$), 2.47 (4H, m, 2 x piperazinyl CH_2), 3.39 (4H, m, 2 x piperazinyl CH_2), 3.66 (2H, s, CH_2N), 6.70 (1H, d, J 8.6Hz, 3'-H), 7.04 (1H, dd, J 7.8, 4.7Hz, 5-H), 7.34 (1H, dd, J 8.6, 2.3Hz, 4'-H), 7.36 (1H, d, J 2.3Hz, 2-H), 7.92 (1H, d, J 2.3Hz, 6'-H), 8.05 (1H, dd, J 7.8, 1.2Hz, 4-H), 8.19 (1H, dd, J 4.7, 1.5Hz, 6-H), and 11.45 (1H, br s, NH); m/z (CI^+, NH_3) 308 $(M+1)^+$.

EXAMPLE 29

3-(4-[4-Hydroxyphenyl]piperazin-1-yl)methyl-1H-pyrrolo[2,3-b]pyridine

M.p. 197-200°C (EtOAc); (Found: C, 68.16; H, 6.46; N, 17.34. $C_{18}H_{20}N_4O.0.5H_2O$ requires C, 68.12; H, 6.67; N, 17.65%); δ_H (DMSO-d_6) 2.93 (4H, t, J 4.3Hz, 2 x piperazinyl CH_2), 3.30-3.32 (4H, m, 2 x piperazinyl CH_2), 3.67 (2H, s, $ArCH_2N$), 6.61-6.63 (2H, m, 2',6'-H), 6.73-6.76 (2H, m, 3',5'-H), 7.04 (1H, dd, J 7.8, 4.7Hz, 5-H), 7.37 (1H, s, 2-H), 8.04 (1H, dd, J 7.8, 1.2Hz, 4-H), 8.19 (1H, dd, J 4.7, 1.2Hz, 6-H), 8.75 (1H, br s, OH), and 11.45 (1H, br s, NH); m/z (CI^+, NH_3) 309 $(M+1)^+$.

EXAMPLE 30

3-(4-(Benzothiophen-2-yl)piperazin-1-yl)methyl-1H-pyrrolo[2,3-b]pyridine

Step 1: 1-Benzyl-4-(benzothiophen-2-yl)piperazine

To a solution of 2-mercaptobenzothiophene (1.8g, 10.8mmol) in toluene under nitrogen was added N-benzylpiperazine (1.88ml, 10.8mmol) and the mixture heated at reflux for 1.5h. Left to cool, concentrated *in vacuo* and product recrystallised from diethyl ether-hexane to yield the *title compound* (1.55g), m.p. 160-161°C.

Step 2: 1-(Benzothiophen-2-yl)piperazine hydrochloride

To a solution of 1-benzyl-4-(benzothiophen-2-yl)piperazine (1.5g, 4.9mmol) in anhydrous dichloromethane (20ml) at 0°C under nitrogen was added 1-chloroethylchloroformate (0.68ml, 6.37mmol). The mixture was allowed to warm to room temperature, stirred for 1h and concentrated *in vacuo*. The crude residue was dissolved in methanol (10ml) and heated to reflux for 30 minutes, left to cool and the *title compound* collected by filtration (0.6g), m.p. 240°C (dec.).

Step 3: 3-(4-(Benzothiophen-2-yl)piperazin-1-yl)methyl-1H-pyrrolo[2,3-b]pyridine

The *title compound* was prepared in an analogous manner to Example 6, Step 3 using 1-(benzothiophen-2-yl)piperazine (180mg, 0.83mmol) and 3-dimethylaminomethyl-1H-pyrrolo[2,3-b]pyridine (145mg, 0.83mmol). Recrystallisation from ethyl acetate-hexane afforded the *title compound* (155mg, 54%), m.p. 269°C (dec.); (Found: C, 69.10; H, 5.85; N, 16.08. $C_{20}H_{20}N_4S$ requires C, 68.94; H, 5.79; N, 16.08%); δ_H (DMSO-d_6) 2.55 (4H, t, J 5Hz, 2 x piperazinyl CH_2), 3.18 (4H, t, J 5Hz, 2 x piperazinyl CH_2), 3.70 (2H, s, indole-CH_2N), 6.26 (1H, s, 3-H-benzothiophene), 7.04 (2H, m, 2 x ArH), 7.19 (1H, m, ArH), 7.05 (2H, m, 2 x ArH), 7.63 (1H, d, 8Hz, ArH), 8.06 (1H, d, 8Hz, ArH), 8.20 (1H, d, 3Hz, ArH), and 11.46 (1H, br s, NH); m/z (CI^+, NH_3) 349 $(M+1)^+$.

EXAMPLE 31

3-(4-(Benzothiophen-3-yl)piperazin-1-yl)methyl-1H-pyrrolo[2,3-b]pyridine

Step 1: 1-(Benzothiophen-3-yl)piperazine

To a solution of methyl 3-aminobenzothiophene-2-carboxylate [prepared by the method of J.R. Beck, J. Org. Chem. 1972, 37, 3224] (6.5g, 31.4mmol) in N-methylpyrrolidinone (30ml) was added 1-methylpiperazine and the reaction mixture was heated to 178°C for 4h. After cooling the mixture was poured into water and the product extracted with diethyl ether (3 x 100ml), the extracts were washed with water (1 x 100ml) and brine (1 x 100ml), combined and dried ($MgSO_4$). Concentration of the extracts yielded

3-aminobenzothiophene (5.9g), which was used without purification. To a solution of 3-aminobenzothiophene (5g, 32mmol) in N-methylpyrrolidinone (50ml) was added piperazine (8.7g, 102mmol) and the mixture heated to reflux under nitrogen for 14h. Cooled and poured into water and extracted with dichloromethane (4 x 100ml). The extracts were washed with brine (50ml), combined and dried ($MgSO_4$). On concentration of the extracts a white solid came out of solution which was collected by filtration to yield the *title compound* (0.78g, more product left in solution); δ_H (DMSO-d_6 + TFA), 3.3 (8H, m, 4 x piperazinyl CH_2), 7.08 (1H, s, 3-H), 7.39 (2H, m, 2 x ArH), 7.83 (1H, m, ArH), 7.95 (1H, m, ArH), and 9.30 (1H, br s, NH).

Step 2: 3-(4-(Benzothiophen-3-yl)piperazin-1-yl)methyl-1H-pyrrolo[2,3-b]pyridine

The *title compound* was prepared in an analogus manner to Example 6, Step 3 using 1-(benzothiophen-3-yl)piperazine (0.5g, 2.3mmol) and 3-dimethylaminomethyl-1H-pyrrole[2,3-b]pyridine (0.40g, 2.3mmol). Recrystallisation using ethyl acetate-hexane afforded the *title compound* (0.18g, 23%), m.p. 172-173°C; (Found: C, 68.37; H, 5.57; N, 15.90. $C_{20}H_{20}N_4S.0.1H_2O$ requires C, 68.58; H, 5.81; N, 16.00%); δ_H (DMSO-d_6) 2.63 (4H, br s, 2 x piperazinyl CH_2), 3.05 (4H, br s, 2 x piperazinyl CH_2), 3.74 (2H, s, indole-$C\underline{H}_2$-N), 6.88 (1H, s, 2-benzothiophene-H), 7.06 (1H, dd, J 8, 2Hz, ArH), 7.39 (3H, m, 3 x ArH), 7.70 (1H, m, ArH), 7.88 (1H, m, ArH), 8.07 (1H, d, J 8Hz, ArH), 8.20 (1H, m, ArH), and 11.48 (1H, br s, NH); m/z (CI^+, NH_3) 349 $(M+1)^+$.

EXAMPLE 32

(±)-3-((1H-Pyrrolo[2,3-b]pyridin-3-yl)methyl)-2,3,4,4a,5,6-hexahydro-1(H)-pyrazino[1,2-a]quinoline

Using the procedure described for Example 1 replacing 1-phenylpiperazine with 2,3,4,4a,5,6-hexahydro-1(H)-pyrazino[1,2-a]quinoline [V.A. Rao *et al.* Indian J. Chem., 7, 833 (1969) and J. Med. Chem., 13, 516 (1970)] the *title compound* was obtained as a colourless solid, m.p. 181-3°C (MeOH); (Found: C, 75.27; H, 6.89; N, 17.50. $C_{20}H_{22}N_4$ requires C, 75.44; H, 6.96; N, 17.60%); δ_H ($CDCl_3$) 1.65-1.9 (2H, m, CH_2CH_2Ar), 1.9-2.05 and 2.2-2.35 (2H, 2m, CH_2CH_2Ar), 2.6-3.1 (6H, m, 3 x CH_2N), 3.65-3.8 (3H, m, indole-CH_2N and CH), 6.75 (1H, t, J 8Hz, 9'-H), 6.8 (1H, d, J 8Hz, 10'-H), 7.0 (1H, d, 8 Hz, 7'-H), 7.05-7.15 (2H, m, 8'-H and 5-H), 7.13 (1H, br s, 2-H), 8.13 (1H, dd, J 8, 1.5 Hz, 4-H), 8.32 (1H, dd, J 4.5, 1.5 Hz, 6-H), and 9.95 (1H, br s, NH).

EXAMPLE 33

(±)-8-Chloro-3-((1H-pyrrolo[2,3-b]pyridin-3-yl)methyl)-2,3,4,4a,5,6-hexahydro-1(H)-pyrazino[1,2-a]quinoline

Step 1: (±)-6-Chloro-2-((1,1-dimethylethoxycarbonylamino)methyl)-1,2,3,4-tetrahydroquinoline

A solution of 6-chloroquinoline-2-carbonitrile (3.4 g, 0.018 mol) in methanol (50 ml) was shaken on a Parr hydrogenator at 55 psi H_2 in the presence of PtO_2 (0.1 g) for 18 h. The catalyst was then removed by filtration and the solvent evaporated. The

residue was dissolved in dichloromethane (100 ml), cooled below -5°C and di-*tert*-butyl dicarbonate (4.5 g, 0.02 mol) was added. After 2h the solvent was evaporated and the residue triturated with hexane to afford the *title compound* as a colourless powder (4.3 g, 80%); δ_H ($CDCl_3$) 1.45 (9H, s, $C(CH_3)_3$), 1.6-1.75 and 1.85-1.95 (2H, 2m, CH_2CH_2Ar), 2.7-2.85 (2H, m, CH_2CH_2Ar), 3.15-3.25, 3.25-3.35, 3.35-3.45 (3H, 3m, $BOCNHCH_2CHN$), 4.88 (1H, br s, NH), 6.48 (1H, d, J 8 Hz, 8-H), 6.91-6.94 (2H, m, 5-H and 7-H).

Step 2: (±)-8-Chloro-2,3,4,4a,5,6-hexahydro-1(H)-pyrazino[1,2-a]quinolin-2-one

A solution of bromoacetyl bromide (3.2 g, 0.016 mol) in dichloromethane (10 ml) was added dropwise to a solution of (±)-6-chloro-2-((1,1-dimethylethoxycarbonylamino)methyl)-1,2,3,4-tetrahydroquinoline (4.3 g, 0.0145 mol) in dichloromethane (90 ml) stirring with aqueous sodium hydroxide [NaOH (0.72g, 0.018 mol); H_2O (10 ml)] cooled below 5°C. After 1h the organic phase was separated, dried ($MgSO_4$) and evaporated to give crude bromoacetamide as a colourless solid (6g) which was used as such.

The bromoacetamide was dissolved in dichloromethane (100 ml). TFA (15 ml) was added and the resulting homogeneous solution was stirred at room temperature for 3h. Tlc (silica; CH_2Cl_2:MeOH:NH_3 90:10:1) after this time showed no remaining starting material with product Rf, 0.1. The solvent and excess reagent were removed *in vacuo* to give the crude amine which was dissolved in DMF (100 ml), powdered potassium carbonate was then added and the resulting slurry was stirred at 80°C under nitrogen for 24h. Tlc (silica; CH_2Cl_2:MeOH:NH_3 90:10:1)

after this time showed product Rf, 0.5 with no remaining starting material. The insolubles were removed by filtration; the mother liquors concentrated *in vacuo* and the residue purified by column chromatography on silica eluting with CH_2Cl_2 then CH_2Cl_2:MeOH (95:5), to afford the *title compound* (1.7 g, 46%) as a buff coloured solid; δ_H ($CDCl_3$) 1.7-2.1 (2H, m, $C\underline{H}_2CH_2Ar$), 2.8-3.05 (2H, m, $CH_2C\underline{H}_2Ar$), 3.4-3.8 (5H, m, $NC\underline{H}_2CO$ and $NCH_2C\underline{H}N$), 7.12 (1H, s, 7-H), 7.15 (1H, d, J 8H, 9-H), and 7.95 (1H, d, J 8Hz, H-10).

Step 3: (±)-8-Chloro-2,3,4,4a,5,6-hexahydro-1(H)-pyrazino[1,2-a]quinoline

Borane-tetrahydrofuran complex (1M, 6 ml) was added dropwise to a solution of 8-chloro-2,3,4,4a,5,6-hexahydro-1(H)-pyrazino[1,2-a]quinolin-2-one (0.5 g, 0.002 mol) in THF (25 ml) stirring at room temperature under nitrogen. The resulting mixture was heated at reflux for 1h, cooled in ice and 1N HCl (20 ml) was added dropwise. The mixture was heated at reflux for 1h. The reaction mixture was then concentrated *in vacuo*, the residue partitioned between CH_2Cl_2:MeOH [1:1] (3 x 20 ml) and ammonia solution (20 ml). The organic phase was evaporated to give crude amine which was purified by column chromatography on silica with CH_2Cl_2:MeOH (9:1) as eluant to afford the *title compound* as a colourless oil (0.34 g, 71%); δ_H ($CDCl_3$) 1.65-1.9 (2H, m, $C\underline{H}_2CH_2Ar$), 2.6-3.2 (8H, m), 3.73-3.8 (1H, m), 6.5 (1H, d, J 8Hz, 10-H), 6.94 (1H, d, J 8 Hz, 9-H), and 6.97 (1H, s, H-7).

Step 4: (±)-8-Chloro-3-((1H-pyrrolo[2,3-b]pyridin-3-yl)methyl)-2,3,4,4a,5,6-hexahydro-1(H)-pyrazino[1,2-a]quinoline

Following the procedure described in Example 6, Step 3 replacing 1-(4-ethoxyphenyl)piperazine with 8-chloro-2,3,4,4a,5,6-hexahydro-1(H)-pyrazino[1,2-a]quinoline the *title compound* was prepared as an off-white solid (24 %), m.p. 203-5°C (MeOH/EtOH); (Found: C, 68.29; H, 5.98; N, 15.79. $C_{20}H_{21}ClN_4$ requires C, 68.07; H, 6.00; N, 15.88%); δ_H (DMSO-d_6) 1.5-1.65, 1.9-2.05 and 2.08-2.15 (4H, 3m, CH_2CH_2Ar), 2.55-3.0 (6H, m, 3 x CH_2N), 3.65-3.8 (3H, m, indole-CH_2N and CH), 6.77 (1H, d, J 8Hz, 9'-H), 6.9-7.1 (3H, m, 10'-H, 7'-H and 5-H), 7.36 (1H, br s, 2-H), 8.03 (1H, dd, J 8, 1.5 Hz, 4-H), 8.2 (1H, dd, J 4.5, 1.5 Hz, 6-H), and 11.5 (1H, br s, NH).

EXAMPLE 34

8-Chloro-3-((1H-pyrrolo[2,3-b]pyridin-3-yl)methyl)-2,3,4,4a,5,6-hexahydro-1(H)-pyrazino[1,2-a]quinoline Enantiomer A

HPLC resolution of the enantiomers of (±)-8-chloro-3-((1H-pyrrolo[2,3-b]pyridin-3-yl)methyl)-2,3,4,4a,5,6-hexahydro-1(H)-pyrazino[1,2-a]quinoline (Example 33) was achieved using a Chiralcel OJ (250x4.6 mm id, 10 micron) column using 10% isopropanol in hexane (+ 0.5% diethylamine) at a flow rate of 1 ml/min. Enantiomer A was first eluting with a retention time of 15.1 min. Preparative HPLC using the above system enabled the isolation of milligram quantities of the *title compound.*

EXAMPLE 35

8-Chloro-3-((1H-pyrrolo[2,3-b]pyridin-3-yl)methyl)-2,3,4,4a,5,6-hexahydro-1(H)-pyrazino[1,2-a]quinoline Enantiomer B

HPLC resolution of the enantiomers of (±)-8-chloro-3-((1H-pyrrolo[2,3-b]pyridin-3-yl)methyl)-2,3,4,4a,5,6-hexahydro-1(H)-pyrazino[1,2-a]quinoline (Example 33) was achieved using a Chiralcel OJ (250x4.6 mm id, 10 micron) column using 10% isopropanol in hexane (+ 0.5% diethylamine) at a flow rate of 1 ml/min. Enantiomer B was second eluting with a retention time of 21.6 min. Preparative HPLC using the above system enabled the isolation of milligram quantities of the *title compound.*

EXAMPLE 36

(±)-8-Chloro-3-((1H-pyrrolo[2,3-b]pyridin-3-yl)methyl)-2,3,4,4a,5,6-hexahydro-1(H)-pyrazino[2,1-c]-1,4-benzoxazine

Step 1: (±)-8-Chloro-2,3,4,4a,5,6-hexahydro-1(H)-pyrazine[2,1-c]-1,4-benzoxazine

Following the procedure of Gupta et al. Indian J. Chem., **13**, 462-7 (1975) replacing 2-nitrophenol with 5-chloro-2-nitrophenol the *title compound* was obtained as a colourless oil; δ_H ($CDCl_3$) 2.45 (1H, dd, J 12, 12Hz, CH), 2.6 (1H, ddd, J, 12, 12, 3Hz, CH), 2.8-3.15 (4H, m, 4 x CH), 3.5 (1H, dd, J 12, 2Hz, CH), 3.9 (1H, dd, J 9, 9Hz, CH), 4.08 (1H, dd, J 12, 2Hz, CH), 6.6 (1H, d, J 8 Hz, 10'-H), 6.7 (1H, d, J 2Hz, 7'-H), and 6.72 (1H, dd, J 8, 2Hz, 9'-H).

Step 2: (±)-8-Chloro-3-((1H-pyrrolo[2,3-b]pyridin-3-yl)methyl)-2,3,4,4a,5,6-hexahydro-1(H)-pyrazino[2,1-c]-1,4-benzoxazine

Following the procedure described in Example 6, Step 3 replacing 1-(4-ethoxyphenyl)piperazine with (±)-8-Chloro-2,3,4,4a,5,6-hexahydro-1(H)-pyrazino[2,1-c]-1,4-benzoxazine the *title compound* was obtained as a colourless solid, m.p.> 200°C (MeOH); (Found: C, 63.98; H, 5.37; N, 15.49. $C_{19}H_{19}ClN_4O$ requires C, 64.31; H, 5.39; N, 15.79%); δ_H (DMSO-d_6) 1.73 (1H, dd, J 11, 2 Hz, CH), 2.14 (1H, dd, J 11, 1.5 Hz, CH), 2.55 (1H, dd, J 11, 2Hz, CH), 2.75-3.0 (3H, m, 3 x CH), 3.6-3.7 (3H, m, 3 x CH), 3.86 (1H, t, J 9Hz, CH), 4.21 (1H, dd, J 10, 3Hz, CH), 6.72 (1H, s, 7'-H), 6.75-6.85 (2H, m, 10'-H and 9'-H), 7.04 (1H, dd, J 8, 4.5Hz, 5-H), 7.38 (1H, br s, 2-H), 8.03 (1H, dd, J 8, 2Hz, 4-H), 8.2 (1H, dd, J 4.5, 2Hz, 6-H), and 11.5 (1H, br s, NH); m/z (CI^+, NH_3) 355, 357 $(M+1)^+$.

EXAMPLE 37

3-(4-[4-Methoxymethylphenyl]piperazin-1-yl)methyl-1H-pyrrolo[2,3-b]pyridine

Step 1: 1-(*tert*-Butoxycarbonyl)-4-(4-trifluoromethanesulfonyloxyphenyl)piperazine

Triethylamine (0.77ml, 5.52mmol) was added to a suspension of 1-(*tert*-butoxycarbonyl)-4-(4-hydroxyphenyl)piperazine (1.39g, 4.99mmol) in dichloromethane and the resulting solution cooled to 0°C. Trifluoromethanesulfonic anhydride (0.92ml, 5.47mmol) was

added and the reaction mixture stirred at 0°C for 1 hour under nitrogen. The mixture was concentrated *in vacuo* to a dark brown oil which was redissolved in dichloromethane (50ml) and washed with 1M hydrochloric acid (50ml), 1M sodium hydroxide solution (50ml) and brine (50ml). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give the *title compound* (1.93g, 94%), as a pale amber oil which crystallised on standing; δ_H ($CDCl_3$) 1.48 (9H, s, $C(CH_3)_3$), 3.16 (4H, m, 2 x piperazinyl CH_2), 3.59 (4H, m, 2 x piperazinyl CH_2), 6.91 (2H, m, ArH), and 7.16 (2H, m, ArH).

Step 2: 1-(*tert*-Butoxycarbonyl)-4-(4-methoxycarbonylphenyl)piperazine

A mixture of 1-(*tert*-butoxycarbonyl)-4-(4-trifluoromethanesulfonyloxyphenyl)piperazine (1.92g, 4.68mmol), palladium (II) acetate (52.5mg, 0.23mmol), 1,1'-bis(diphenylphosphino)ferrocene (325.0mg, 0.59mmol), triethylamine (1.3ml, 9.33mmol), methanol (8ml) and dimethylformamide (20ml) was purged with carbon monoxide for 15 minutes, sealed under a balloon of carbon monoxide and stirred at 60°C overnight (18 hours). The reaction mixture was allowed to cool, concentrated *in vacuo* to a small volume and the residue triturated with ethyl acetate. The solid was collected, washed with ethyl acetate and dried to give the *title compound* (0.659g, 44%), as a pale cream solid. Evaporation of the ethyl acetate mother liquors and purification of the residue by flash chromatography (eluting with 5% to 10% ethyl acetate in dichloromethane) gave more of the *title compound* (0.492g, 33%); δ_H ($CDCl_3$) 1.49 (9H, s, $C(CH_3)_3$), 3.31 (4H, m, 2 x piperazinyl CH_2), 3.60 (4H, m, 2 x piperazinyl CH_2), 3.87 (3H, s, CO_2CH_3), 6.89 (2H, m, ArH), and 7.94 (2H, m, ArH).

Step 3: 1-(*tert*-Butoxycarbonyl)-4-(4-hydroxymethylphenyl)piperazine

Diisobutylaluminium hydride in toluene (1.5M, 15ml, 22.5mmol) was added dropwise to a solution of 1-(*tert*-butoxycarbonyl)-4-(4-methoxycarbonylphenyl)piperazine (2.90g, 9.05mmol) in THF (116ml) at 0°C. The mixture was stirred at 0°C for 2 hours then allowed to warm to room temperature. The solution was recooled to -4°C and the reaction quenched by the addition of methanol (6ml), water (3ml) and finally 2M sodium hydroxide (3ml). The mixture was allowed to warm to room temperature, the precipitated aluminium salts collected under suction and washed with dichloromethane. The filtrate was concentrated *in vacuo* and the residue purified by flash chromatography, eluting with dichloromethane/ethyl acetate, to give the *title compound* (2.30g, 74%); δ_H ($CDCl_3$) 1.48 (9H, s, $C(CH_3)_3$), 1.60 (1H, v br, CH_2OH), 3.13 (4H, m, 2 x piperazinyl CH_2), 3.58 (4H, m, 2 x piperazinyl CH_2), 4.61 (2H, s, CH_2OH), 6.92 (2H, m, ArH), and 7.29 (2H, m, ArH).

Step 4: 1-(*tert*-Butoxycarbonyl)-4-(4-methoxymethylphenyl)piperazine

Sodium hydride (80% dispersion in oil; 0.10g, 3.3mmol) was added to a solution of (1-*tert*-butoxycarbonyl)-4-(4-hydroxymethylphenyl)piperazine (0.80g, 2.74mmol) in THF (10ml) at 0°C. The mixture was stirred at 0°C for 90 minutes, allowed to warm to room temperature and stirred for a further 30 minutes. The mixture was recooled to 0°C, methyl iodide (0.20ml, 3.2mmol) added dropwise and the mixture stirred at room temperature overnight. TLC indicated that starting material remained unreacted. A further portion of sodium hydride (0.04g, 1.3mmol)

was added, the reaction mixture stirred at room temperature for one hour, methyl iodide (0.17ml, 2.73mmol) was added and the mixture stirred overnight. The reaction mixture was poured into water (100ml) and extracted with ethyl acetate (2 x 50ml). The extracts were washed with brine (50ml), combined, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography eluting with ethyl acetate/petrol (60-80°) to give the *title compound* (0.62g, 74%); δ_H (DMSO-d_6) 1.42 (9H, s, $C(CH_3)_3$), 3.08 (4H, m, 2 x piperazinyl CH_2), 3.22 (3H, s, $CH_2OC\underline{H}_3$), 3.45 (4H, m, 2 x piperazinyl CH_2), 4.28 (2H, s, $ArC\underline{H}_2OCH_3$), 6.92 (2H, m, ArH), and 7.17 (2H, m, ArH).

Step 5: 1-(4-Methoxymethylphenyl)piperazine

A solution of hydrogen chloride in ether (10ml) was added to a solution of 1-(*tert*-butoxycarbonyl)-4-(4-methoxymethylphenyl)piperazine (0.62g, 2.02mmol) in ethyl acetate (10ml) and the resulting mixture stirred at room temperature for 15 minutes. The mixture was poured into saturated aqueous potassium carbonate (200ml) and extracted with dichloromethane (2 x 100ml). The extracts were washed with brine (100ml), combined, dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography, eluting with 90:8:1 then 60:8:1 dichloromethane/methanol/ammonia, to give the *title compound* (0.26g, 62%), as a pale brown oil; δ_H ($CDCl_3$) 3.03 (4H, m, 2 x piperazinyl CH_2), 3.14 (4H, m, 2 x piperazinyl CH_2), 3.34 (3H, s, $CH_2OC\underline{H}_3$), 4.37 (2H, s, $ArC\underline{H}_2OCH_3$), 6.90 (2H, m, ArH), and 7.23 (2H, m, ArH).

Step 6: 3-(4-[4-Methoxymethylphenyl]piperazin-1-yl)methyl-1H-pyrrolo[2,3-b]pyridine

1-(4-Methoxymethylphenyl)piperazine was converted into the *title compound* by the method outlined in Example 6, Step 3.

M.p. 161.5-163°C (MeOH); (Found: C, 71.46; H, 7.07; N, 16.09. $C_{20}H_{24}N_4O.0.06\ C_7H_8$ requires C, 71.72; H, 7.22; N, 16.38%); δ_H (DMSO-d_6) 2.52 (4H, m, 2 x piperazinyl CH_2), 3.10 (4H, m, 2 x piperazinyl CH_2), 3.21 (3H, s, $CH_2OC\underline{H}_3$), 3.68 (2H, s, CH_2N), 4.26 (2H, s, $ArC\underline{H}_2OCH_3$), 6.87 (2H, d, J 8.6Hz, ArH), 7.04 (1H, dd, J 7.8, 4.6Hz, 5-H), 7.13 (2H, d, J 8.6Hz, ArH), 7.37 (1H, br s, 2-H), 8.05 (1H, br d, J 7.8Hz, 4-H), 8.19 (1H, dd, J 4.6, 1.4Hz, 6-H), and 11.47 (1H, br s, NH); m/z (CI^+, NH_3) 337 (M+1).

EXAMPLE 38

3-(4-[4-Dimethylaminomethylphenyl]piperazin-1-yl)methyl-1H-pyrrolo[2,3-b]pyridine

Step 1: 1-(4-Dimethylcarboxamidophenyl)piperazine

A mixture of 1-(*tert*-butoxycarbonyl)-4-(4-trifluoromethanesulfonyloxyphenyl)piperazine (7.4g, 18mmol), palladium(II) acetate (198mg, 0.88mmol), 1,1'-bis(diphenylphosphino)ferrocene (1.28g, 2.25mmol), triethylamine (17.6ml, 126mmol), dimethylamine hydrochloride (7.3g, 90mmol) and dimethylformamide (75ml) was purged with carbon monoxide for 15 minutes, sealed under a balloon of carbon monoxide and stirred at 60°C overnight (20 hours). The reaction was cooled and concentrated *in vacuo* to a small volume. Water (50ml) and ethyl acetate (50ml) were added and the phases were separated. The aqueous was extracted with ethyl acetate (2 x 50ml). The combined

organics were washed with water (20ml) and brine (20ml), dried ($MgSO_4$) and evaporated *in vacuo* to give a purple residue. The crude product was chromatographed on silica eluting with 2% methanol/dichloromethane. The amine was deprotected by dissolving the compound in ethyl acetate and treatment with ethereal hydrogen chloride. The gum obtained was partitioned between hydrochloric acid (0.5M) and ether, the phases were separated and the aqueous washed again with ether. The aqueous was basified with sodium hydroxide (10M) and extracted with n-butanol (4 x 50ml). The extracts were dried (Na_2SO_4) and evaporated *in vacuo* to give the *title compound* as a brown gum (0.8g, 19%); δ_H ($CDCl_3$) 2.98-3.14 (8H, m, $N(CH_3)_2$ and piperazinyl CH_2), 3.18-3.30 (4H, m, 2 x piperazinyl CH_2), 3.56-3.65 (2H, m, piperazinyl CH_2), 6.89 (2H, d, J 12.5Hz, ArH), and 7.40 (2H, d, J 12.5Hz, ArH).

Step 2: 3-(4-[4-Dimethylcarboxamidophenyl]piperazin-1-yl)methyl-1H-pyrrolo[2,3-b]pyridine

1-(4-Dimethylcarboxamidophenyl)piperazine was converted into the *title compound* by the method outlined in Example 6, Step 3; m.p. 217-219°C (MeOH).

Step 3: 3-(4-[4-Dimethylaminomethylphenyl]piperazin-1-yl)methyl-1H-pyrrolo[2,3-b]pyridine

Lithium aluminium hydride (1M solution in THF, 2.7ml, 2.7mmol) was carefully added to a suspension of 3-(4-[4-dimethyl-carboxamidophenyl]piperazin-1-yl)methyl-1H-pyrrolo[2,3-b]pyridine (650mg, 1.79mmol) in tetrahydrofuran (30ml) under a nitrogen

atmosphere and the resultant solution was heated at reflux for 2 hours.

The mixture was cooled to room temperature and treated with water (0.1ml), sodium hydroxide (4N, 0.1ml) and water (0.3ml). The mixture was filtered through celite® and the filter cake was washed with tetrahydrofuran. The filtrate was evaporated *in vacuo* and the residue triturated with ether. Recrystallisation from ethyl acetate gave the *title compound* as an off white solid (228mg, 36%), m.p. 163-165°C; (Found: C, 71.72; H, 7.90; N, 20.02. $C_{21}H_{27}N_5.0.2$ (H_2O) requires C, 71.80; H, 7.81; N, 19.93%); δ_H (DMSO-d_6) 2.08 (6H, s, $N(CH_3)_2$), 2.49-2.53 (4H, m, 2 x piperazinyl CH_2), 3.07 (4H, m, 2 x piperazinyl CH_2), 3.24 (2H, s, $ArCH_2N(CH_3)_2$), 3.67 (2H, s, $ArCH_2N$), 6.84 (2H, d, J 8.6Hz, 2 x ArH), 7.02-7.09 (3H, m, ArH), 7.37 (1H, d, J 2.1Hz, 2-H), 8.04 (1H, dd, J 7.8, 1.2Hz, 4-H), 8.18 (1H, dd, J 4.6, 1.5Hz, 6-H), and 11.47 (1H, br s, NH); m/z (CI^+, NH_3) 350 $(M+1)^+$.

EXAMPLE 39

3-(1,2,3,4,10,10a-Hexahydropyrazino[1,2-a]indol-2-yl)methyl-1H-pyrrolo[2,3-b]pyridine

Step 1: 1,2,3,4,10,10a-Hexahydropyrazino[1,2-a]indole

Palladium on charcoal (10%, 660mg) was carefully added to a solution of 2-benzyl-1,2,3,4-tetrahydropyrazino[1,2-a]indole hydrochloride (4.2g, 140mmol) (prepared using the method of Freed, US Patent 3,317,524) in methanol (200ml) under a nitrogen atmosphere and the mixture was hydrogenated at 45 psi, 50°C for 3.5 hours after which time the hydrogen uptake had ceased. The catalyst was removed by filtration and the filtrate concentrated *in vacuo* to about 50ml. Dry ether (100ml) was added, the precipitated

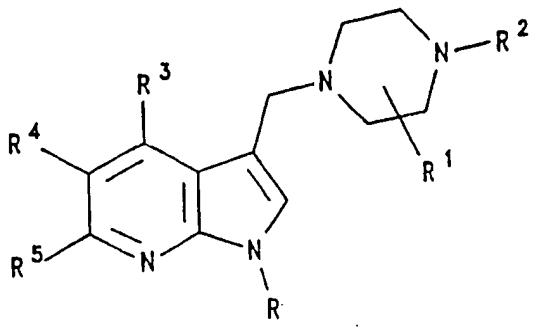
pink solid was collected by filtration and dried *in vacuo*. This hydrochloride salt was partitioned between sodium hydroxide solution (2N, 100ml) and ethyl acetate (100ml), the phases were separated and the aqueous extracted with ethyl acetate (100ml and 50ml). The combined organics were washed with brine (50ml), dried (Na_2SO_4) and evaporated *in vacuo* to give a red oil. The oil was purified by column chromatography on silica eluting with 10% methanol/dichloromethane to give 1,2,3,4-tetrahydropyrazine [1,2-a]indole (1.48g, 61%) and 1,2,3,4,10,10a-hexahydropyrazino[1,2,-a]indole (280mg, 11%); δ_H ($CDCl_3$) 2.53-2.60 (1H, m, aliphatic CH), 2.78-3.17 (6H, m, 3 x aliphatic CH_2), 3.47-3.71 (2H, m, aliphatic CH_2), 6.45 (1H, t, J 7.7Hz, ArH), 6.64-6.68 (1H, m, ArH), and 7.05-7.09 (2H, m, ArH).

Step 2: 3-(1,2,3,4,10,10a-Hexahydropyrazino[1,2-a]indol-2-yl)methyl-1H-pyrrolo[2,3-b]pyridine

Following the procedure described in Example 6, Step 3 replacing 1-(4-ethoxyphenyl)piperazine with 1,2,3,4,10,10a-hexahydropyrazino[1,2-a]indole the *title compound* was obtained, m.p. 197-198°C (EtOAc); (Found: C, 74.53; H, 6.77; N, 17.86. $C_{19}H_{20}N_4.0.05$ ($CH_3CO_2C_2H_5$) requires C, 74.68; H, 6.66; N, 18.14%); δ_H (DMSO-d_6) 1.91-1.98 (1H, m, 1 x aliphatic H), 2.05 (1H, dt, J 3.0, 11.3Hz, 1 x aliphatic H), 2.43 (1H, m, 1 x aliphatic H), 2.76-2.90 (4H, m, 4 x aliphatic H), 3.42-3.69 (4H, m, 4 x aliphatic H), 6.43-6.53 (2H, m, ArH), 6.92-7.05 (3H, m, ArH), 7.34 (1H, d, J 2.2Hz, 2-H), 8.03 (1H, dd, J 7.8, 1.3Hz, 4-H), 8.18 (1H, dd, J 4.6, 1.4Hz, 6-H), and 11.47 (1H, br s, NH); m/z (CI^+, NH_3) 305 $(M+1)^+$.

CLAIMS:

1. The use of a compound of formula I, or a pharmaceutically acceptable salt thereof or a prodrug thereof:



(I)

wherein

R represents hydrogen or C_{1-6} alkyl;

R^1 represents hydrogen, or an optionally substituted C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, aryl(C_{1-6})alkyl, aryloxy(C_{1-6})alkyl, aryl(C_{1-6})alkoxy, aryl(C_{2-6})alkenyl, aryl(C_{2-6})alkynyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl, heteroaryl(C_{1-6})alkyl, heteroaryl(C_{2-6})alkenyl or heteroaryl(C_{2-6})alkynyl group; or R^1 represents a straight or branched alkylene chain containing from 1 to 4 carbon atoms, and optionally incorporating an oxygen atom, which links the piperazine moiety to the group R^2;

R^2 represents an optionally substituted C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, aryl(C_{1-6})alkyl, aryloxy(C_{1-6})alkyl, aryl(C_{1-6})alkoxy, aryl(C_{2-6})alkenyl, aryl(C_{2-6})alkynyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl, heteroaryl(C_{1-6})alkyl, heteroaryl(C_{2-6})alkenyl or heteroaryl(C_{2-6})alkynyl group;

R^3, R^4 and R^5 independently represent hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, nitro, $-OR^a$, $-SR^a$, $-SOR^a$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aR^b$, $-NR^aCOR^b$, $-NR^aCO_2R^b$, $-COR^a$, $-CO_2R^a$ or $-CONR^aR^b$; and

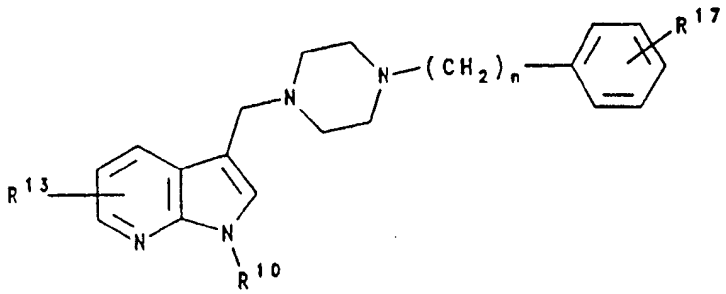
R^a and R^b independently represent hydrogen, hydrocarbon or a heterocyclic group;

for the manufacture of a medicament for the treatment and/or prevention of psychotic disorders.

2. The use as claimed in claim 1 wherein R^1 represents hydrogen, or an optionally substituted C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, aryl(C_{1-6})alkyl, aryloxy(C_{1-6})alkyl, aryl(C_{1-6})alkoxy, aryl(C_{2-6})alkenyl, aryl(C_{2-6})alkynyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl, heteroaryl(C_{1-6})alkyl, heteroaryl(C_{2-6})alkenyl or heteroaryl(C_{2-6})alkynyl group; and

R^2, R^3, R^4 and R^5 are as defined in claim 1.

3. The use as claimed in claim 1 or claim 2 of a compound represented by formula IIA, and pharmaceutically acceptable salts thereof and prodrugs thereof:



(IIA)

wherein

n is zero, 1, 2 or 3;

R^{10} represents hydrogen or methyl;

R^{13} represents hydrogen, halogen, cyano, nitro, trifluoromethyl, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, C_{1-6} alkyl, C_{1-6} alkoxy, aryl(C_{1-6})alkoxy or C_{2-6} alkylcarbonyl; and

R^{17} represents hydrogen, C_{1-6} alkyl, halogen, trifluoromethyl, hydroxy, hydroxy(C_{1-6})alkyl, C_{1-6} alkoxy, aryl(C_{1-6})alkoxy, C_{1-6} alkoxy(C_{1-6})alkyl, carboxy, C_{2-6} alkoxycarbonyl, C_{2-6} alkylcarbonyl, cyano, nitro, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, amino(C_{1-6})alkyl, C_{1-6} alkylamino(C_{1-6})alkyl or di(C_{1-6})alkylamino(C_{1-6})alkyl.

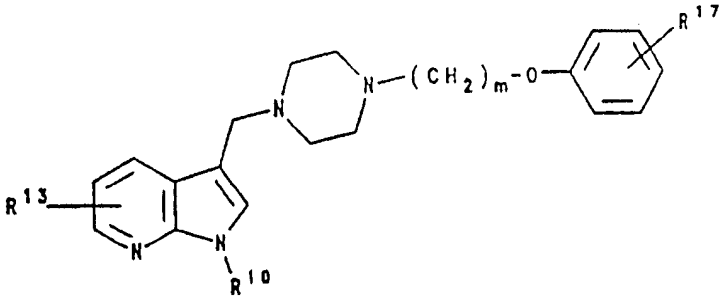
4. A method for the treatment and/or prevention of psychotic disorders, which comprises administering to a patient in need of such treatment an effective amount of a compound of formula I as defined in claim 1, or a pharmaceutically acceptable salt thereof or a prodrug thereof.

5. The method as claimed in claim 4 wherein R^1 represents hydrogen, or an optionally substituted C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, aryl(C_{1-6})alkyl, aryloxy(C_{1-6})alkyl, aryl(C_{1-6})alkoxy, aryl(C_{2-6})alkenyl, aryl(C_{2-6})alkynyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl, heteroaryl(C_{1-6})alkyl, heteroaryl(C_{2-6})alkenyl or heteroaryl(C_{2-6})alkynyl group; and

R, R^2, R^3, R^4 and R^5 are as defined in claim 1.

6. The method as claimed in claim 4 wherein the compound administered is represented by formula IIA as defined in claim 3, and pharmaceutically acceptable salts thereof and prodrugs thereof.

7. A compound of formula IIB, or a salt thereof or a prodrug thereof:



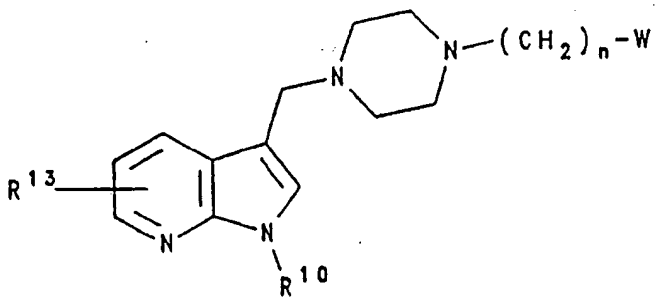
(IIB)

wherein

m is 1, 2 or 3; and

R^{10}, R^{13} and R^{17} are as defined in claim 3.

8. A compound of formula IIC, or a salt thereof or a prodrug thereof:

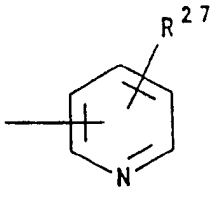


(IIC)

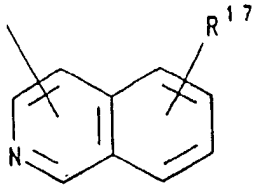
wherein

n, R^{10} and R^{13} are as defined in claim 3; and

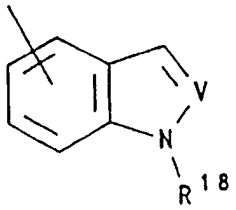
W represents a group of formula (i), (ii), (iii) or (iv):



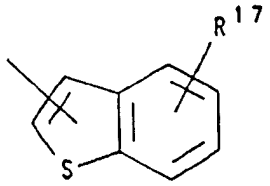
(I)



(II)



(III)



(IV)

in which

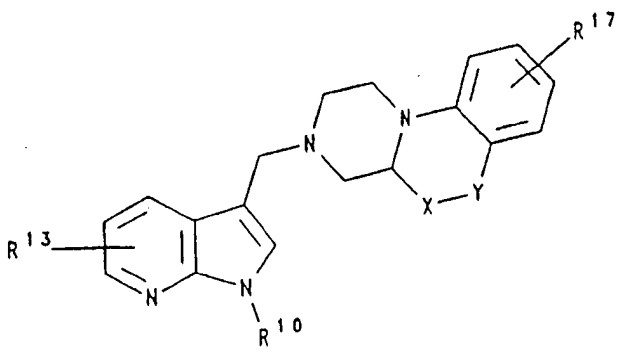
V represents nitrogen or CH;

R^{17} is as defined in claim 3;

R^{18} represents hydrogen or methyl; and

R^{27} represents C_{1-6} alkyl, halogen, trifluoromethyl, C_{1-6} alkoxy, cyano, nitro, amino, C_{1-6} alkylamino or di(C_{1-6})alkylamino.

9. A compound of formula IID, or a salt thereof or a prodrug thereof:



(IID)

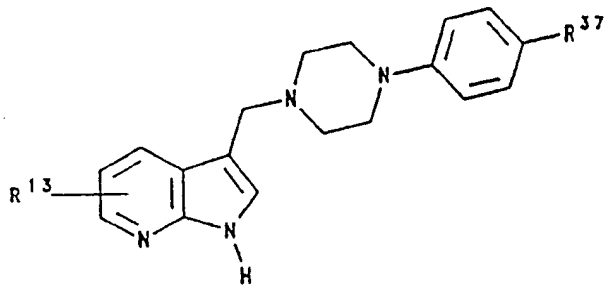
wherein

X represents a group of formula $-CH_2-$ or $-CH_2CH_2-$;

Y represents a chemical bond or an oxygen atom; and

R^{10}, R^{13} and R^{17} are as defined in claim 3.

10. A compound of formula IIE, or a salt thereof or a prodrug thereof:



(IIE)

wherein

R^{13} is as defined in claim 3; and

R^{37} represents fluoro, chloro, bromo, iodo or trifluoromethyl.

11. A compound selected from:

3-(4-phenylpiperazin-1-yl)methyl-1H-pyrrolo[2,3-b]-pyridine;

3-[4-(4-methoxyphenyl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;

3-(4-benzylpiperazin-1-yl)methyl-1H-pyrrolo[2,3-b]-pyridine;

3-[4-(4-ethylphenyl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;

3-[4-(4-chlorophenyl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;

and salts and prodrugs thereof.

12. A compound selected from:

3-[4-(4-ethoxyphenyl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;

3-[4-(4-dimethylaminophenyl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;

3-[4-(3,4-dichlorophenyl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;

3-[4-(4-methoxyphenyl)piperazin-1-yl]methyl-1-methyl-1H-pyrrolo[2,3-b]pyridine;

3-[4-(5-chloropyrid-2-yl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;

3-[4-(3-isoquinolyl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;

3-[4-(5-indolyl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;

3-[4-(4-iodophenyl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;

3-[4-(4-trifluoromethylphenyl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;

3-[4-(2-phenoxyethyl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;

3-[4-(4-methylphenyl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;

and salts and prodrugs thereof.

13. A compound selected from:

3-[4-(4-fluorophenyl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;

3-[4-(1-methylindol-5-yl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;

3-[4-(indazol-5-yl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;

3-[4-(4-ethoxycarbonylphenyl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;

3-[4-(4-carboxyphenyl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;

3-[4-(3-methylphenyl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(2-methylphenyl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(3,4-methylenedioxyphenyl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(4-bromophenyl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(4-methoxycarbonylphenyl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(4-hydroxymethylphenyl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(5-methylpyrid-2-yl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(4-hydroxyphenyl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(benzothiophen-2-yl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(benzothiophen-3-yl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[(1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]-2,3,4,4a,5,6-hexahydro-1(H)-pyrazino[1,2-a]quinoline;
8-chloro-3-[(1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]-2,3,4,4a,5,6-hexahydro-1(H)-pyrazino[1,2-a]quinoline;
8-chloro-3-[(1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]-2,3,4,4a,5,6-hexahydro-1(H)-pyrazino[2,1-c]-1,4-benzoxazine;
3-[4-(4-methoxymethylphenyl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(4-dimethylaminomethylphenyl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-(1,2,3,4,10,10a-hexahydropyrazino[1,2-a]indol-2-yl)methyl-1H-pyrrolo[2,3-b]pyridine;
and salts and prodrugs thereof.

14. 3-[4-(4-Chlorophenyl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine; and salts and prodrugs thereof.

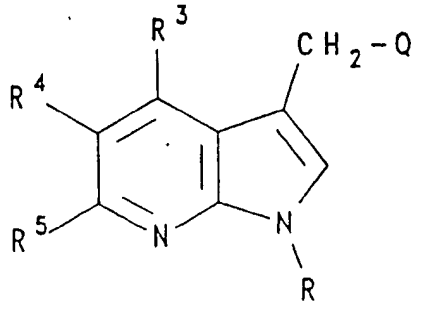
15. A pharmaceutical composition comprising a compound as claimed in any one of claims 7 to 14 in association with a pharmaceutically acceptable carrier.

16. A compound as claimed in any one of claims 7 to 14 for use in therapy.

17. The use of a compound as claimed in any one of claims 7 to 14 for the manufacture of a medicament for the treatment and/or prevention of psychotic disorders.

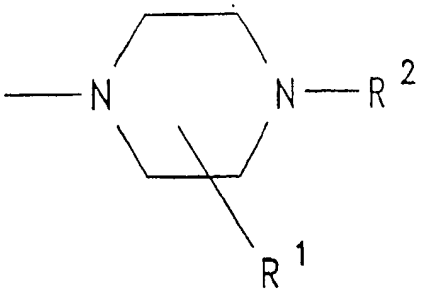
18. A method for the treatment and/or prevention of psychotic disorders, which comprises administering to a patient in need of such treatment an effective amount of a compound as claimed in any one of claims 7 to 14.

19. A process for the preparation of a compound of formula IA:

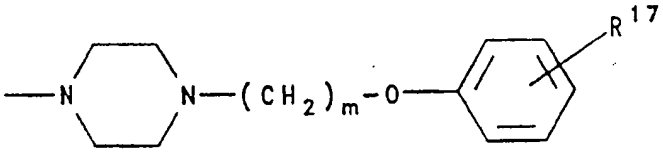


(IA)

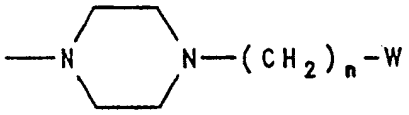
wherein R, R^3, R^4 and R^5 are as defined in claim 1, and Q represents a group of formula



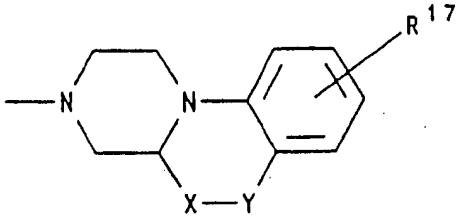
selected from the moieties of formula Qa, Qb, Qc and Qd:



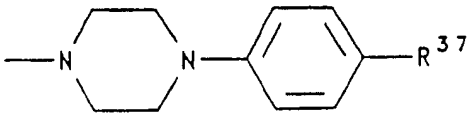
(Qa)



(Qb)



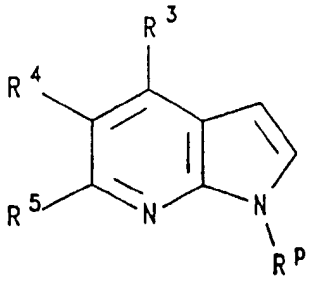
(Qc)



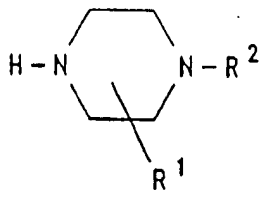
(Qd)

in which n and R^{17} are as defined in claim 3, m is as defined in claim 7, W is as defined in claim 8, X and Y are as defined in claim 9 and R^{37} is as defined in claim 10; which process comprises:

(A) reacting a compound of formula III with a compound of formula IV:



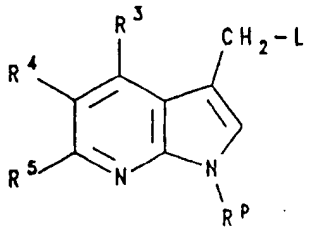
(III)



(IV)

wherein R^P corresponds to the group R or represents a suitable protecting group; in the presence of a substantially equimolar amount of formaldehyde; followed, where required, by removal of the protecting group R^P; and subsequently, if necessary, N-alkylation by standard methods to introduce the moiety R; or

(B) reacting a compound of formula IV as defined above with a compound of formula V:



(V)

wherein L represents a suitable leaving group; followed, where required, by removal of the protecting group R^P; and subsequently, if necessary, N-alkylation by standard methods to introduce the moiety R; and

(C) subsequently, where required, converting a compound of formula IA initially obtained into a further compound of formula IA by conventional methods.

20. A process as claimed in claim 19 wherein L represents a halogen atom or a dialkylamino group.

21. A process for the preparation of a pharmaceutical composition which comprises mixing a compound as claimed in any one of claims 7 to 14 with a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 94/00337

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07D471/04 A61K31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,3 362 956 (S. ARCHER) cited in the application see examples 3,14 ---	1-18
A	US,A,3 511 841 (S. ARCHER) 12 May 1970 cited in the application see examples 8,10 -----	1-18

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance

'E' earlier document but published on or after the international filing date

'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 June 1994	20. 07. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Frelon, D

INTERNATIONAL SEARCH REPORT

International application No. PCT/GB94/00337

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 4, 5, 6 and 18 are directed to a method of treatment of (diagnostic method practised on) the human/animal body (Rule 39.1.(iv),PCT) the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 94/00337

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-3362956		US-A- 3472854	14-10-69
US-A-3511841	12-05-70	NONE	